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(54) Fused pyrimidine derivatives, process and intermediates for their preparation and pharmaceutical compositions containing them.

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GB-A- 1 543 874

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Descripti n

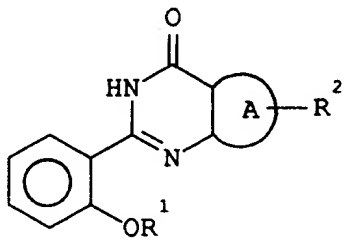
The present invention relates to fused pyrimidine derivatives, processes for their preparation, intermediates in their preparation, their use as therapeutic agents and to pharmaceutical compositions containing them. The compounds of this invention are inhibitors of a calmodulin insensitive cyclic GMP phosphodiesterase and are of use in combating such conditions where such inhibition is thought to be beneficial. They are bronchodilators and are therefore of use in combating chronic reversible obstructive lung diseases such as asthma and bronchitis. Some of the compounds of the present invention have anti-allergic activity and are therefore useful in combating allergic diseases such as allergic asthma, allergic rhinitis, urticaria and irritable bowel syndrome. Furthermore the compounds of this invention are vasodilators and are therefore of value in combating angina, hypertension and congestive heart failure.

GB-A-1,543,874 (Carlo Erba) discloses a series of substituted phenyl-3,4-dihydro-4-oxo-quinazoline derivatives which are said to possess anti-allergic activity.

FR-A-2,225,166 (Pfizer) discloses bicyclic and tricyclic ring systems containing a pyrimidine moiety as anti-allergic agents.

DE-A-1,795,722 (Karl Thomae) discloses substituted pyrimido[5,4-d]pyrimidines which act as cardiovascular agents.

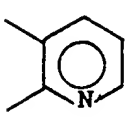
Accordingly, the present invention provides compounds of the formula (1):



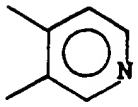
(1)

and pharmaceutically acceptable salts thereof, wherein

is a ring of sub-formula (a), (b), (c), (d), (e), (f) or (g) :



(a)



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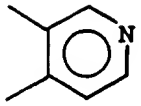

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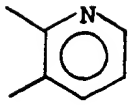
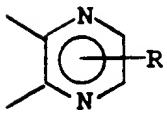
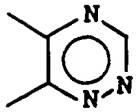


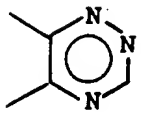
(d)



(e)



(f)



(g)

R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-6}alkyl, or C_{1-6}alkyl substituted by 1 to 6 fluoro groups;

R^2 is C_{1-6}alkylthio, C_{1-6}alkylsulphonyl, C_{1-6}alkoxy, hydroxy, hydrogen, hydrazino, C_{1-6}alkyl, phenyl, $-NHCOR^3$ wherein R^3 is hydrogen or C_{1-6}alkyl, or $-NR^4R^5$, wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring, or R^4 and R^5 are independently hydrogen, C_{3-5}cycloalkyl or C_{1-6}alkyl which is optionally substituted by $-CF_3$, phenyl, $-S(O)_nC_{1-6}$-alkyl wherein n is 0, 1 or 2, $-OR^6$, $-CO_2R^7$ or $-NR^8R^9$ wherein R^6 to R^9 are independently hydrogen or C_{1-6}alkyl, provided that the carbon atom adjacent to the nitrogen atom is not substituted by said $-S(O)_nC_{1-6}$alkyl, $-OR^6$ or $-NR^8R^9$ groups; and

R is hydrogen and can also be hydroxy when R^2 is hydroxy.

Suitably R^1 is C_{2-5}alkyl for example ethyl, n-propyl, isopropyl, butyl, isobutyl or pentyl.

Suitably R^1 is C_{3-5}alkenyl for example propenyl, butenyl or pentenyl.

Suitably R^1 is cyclopropylmethyl.

Examples of C_{1-6}alkyl substituted by 1 to 6 fluoro groups include $-CF_3$, $-CH_2CF_3$ or $-CF_2CHFCF_3$.

Preferably R^1 is n-propyl.

Suitably R^2 is C_{1-6}alkylthio, C_{1-6}alkylsulphonyl or C_{1-6}alkoxy for example methylthio, ethylthio, methylsulphonyl, ethylsulphonyl, methoxy, ethoxy or propoxy.

Suitably R^2 is hydroxy, hydrogen or hydrazino.

Suitably R^2 is phenyl or C_{1-6}alkyl for example methyl, ethyl or propyl.

Suitably R^2 is $-NHCOR^3$ for example formamido or acetamido.

Suitably R^2 is $-NR^4R^5$ for example amino, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, dipropylamino, cyclopropylamino, morpholino, 2,2,2-trifluoroethylamino, phenethylamino, 3-methylthiopropylamino, 3-methylsulphinylpropylamino, 3-methylsulphonylpropylamino, 2-hydroxyethylamino, 3-hydroxypropylamino, 2-hydroxypropylamino, 3-methoxypropylamino, N-ethyl-N-(2-hydroxyethyl)amino, 2-aminoethylamino, 2-dimethylaminoethylamino, ethoxycarbonylmethylamino, carboxymethylamino, 2-ethoxycarbonylethylamino or 2-carboxyethylamino.

Suitably

is a group of sub-formula (a) thus forming a pyrido[2,3-d]pyrimidine ring system.

Suitably

is a group of sub-formula (b) thus forming a pyrido[3,4-d]pyrimidine ring system.
Suitably

is a group of sub-formula (c) thus forming a pyrido[4,3-d]pyrimidine ring system.
Suitably

is a group of sub-formula (d) thus forming a pyrido[3,2-d]pyrimidine ring system.
Suitably

is a group of sub-formula (e) thus forming a pteridine ring system.
Suitably

is a group of sub-formula (f) thus forming a pyrimido[5,4-e][1,2,4]triazine ring system.
Suitably

is a group of sub-formula (g) thus forming a pyrimido[4,5-e][1,2,4]triazine ring system.
Particular compounds of this invention are :
2-(2-propoxyphenyl)pyrido[2,3-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pyrido[3,4-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pyrido[4,3-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pyrido[3,2-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pteridin-4(3H)-one,
2-(2-propoxyphenyl)pteridin-4,6(3H,5H)-dione,
2-(2-propoxyphenyl)pteridin-4,6,7(3H,5H,8H)-trione,
5,6-dihydro-3-methylthio-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine,
3-amino-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine,
3-methylamino-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine,
3-methoxy-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine,
3-methylthio-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-amino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methylamino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methoxy-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,

3,8-dioxo-6-(2-propoxyphenyl)-3,4,7,8-tetrahydropyrimido[4,5-e][1,2,4]triazine,
3-dimethylamino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methylthio-8-oxo-6-(2-allyloxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methylthio-8-oxo-6-(2-isobutoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methylthio-8-oxo-6-(2-cyclopropylmethoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine or
3-methylthio-8-oxo-6-(2-methoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine
or pharmaceutically acceptable salts thereof.

This invention covers all tautomeric and optical isomeric forms of compounds of formula (1).

Compounds of the formula (1) wherein R^2 is $-NR^4R^5$ or hydrazino may form pharmaceutically acceptable salts with acids such as hydrochloric, hydrobromic, sulphuric, methanesulphonic and phosphoric acids.

Compounds of the formula (1) may form pharmaceutically acceptable salts with metal ions, such as alkali metals for example sodium and potassium, or with an ammonium ion.

In order to use a compound of the formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of formula (1) and their pharmaceutically acceptable salts may be administered in standard manner for the treatment of the indicated diseases, for example orally, sublingually, parenterally, transdermally, rectally, via inhalation or via buccal administration.

Compounds of formula (1) and their pharmaceutically acceptable salts which are active when given orally or via buccal administration can be formulated appropriately in dosage forms such as liquids, syrups, tablets, capsules and lozenges. An oral liquid formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include starch, celluloses, lactose, sucrose and magnesium stearate. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule, any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil or solubilising agent, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, 2-pyrrolidone, cyclodextrin, arachis oil, or sesame oil.

A typical suppository formulation comprises a compound of formula (1) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be adminstered in the form of an aerosol using a conventional propellant such as dichlorodifluoromthane or trichlorofluoromethane, or are in the form of a power for insufflation.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to himself a single dose.

Each dosage unit for oral administration contains suitably from 0.001 mg/Kg to 30 mg/Kg, and preferably from 0.005 mg/Kg to 15 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.001 mg/Kg to 10 mg/Kg, of a compound of formula (1) or a pharmaceutically acceptable salt thereof calculated as the free base.

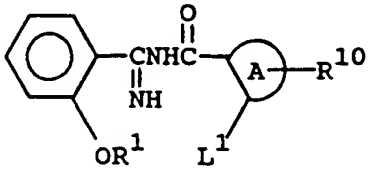
The daily dosage regimen for oral adminstration is suitably about 0.001 mg/Kg to 120 mg/Kg, of a compound of formula (1) or a pharmaceutically acceptable salt thereof calculated as the free base. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, for example about 0.005 mg/Kg to 10 mg/Kg , of a compound of the formula (1) or a pharmaceutically acceptable salt thereof calculated as the free base. The active ingredient may be administered as required for example from 1 to 8 times a day or by infusion. The compositions of the invention are bronchodilators and are useful in chronic reversible obstructive lung disease for example asthma and bronchitis. In addition some of the compositions of the present invention have anti-allergic activity and are useful in combatting allergic diseases such as allergic asthma, allergic rhinitis, urticaria and irritable bowel syndrome. The compositions

of the present invention also have vasodilator activity and are of use in the treatment of angina, hypertension and congestive heart failure. Such conditions can be treated by administration orally, sublingually topically, rectally, parenterally or by inhalation. For administration by inhalation dosages are controlled by a valve, are administered as required and for an adult are conveniently in the range 0.1-5.0 mg of a compound of the formula (1) or a pharmaceutically acceptable salt thereof.

The compounds of this invention may be co-administered with other pharmaceutically active compounds, for example in combination, concurrently or sequentially. Conveniently the compounds of this invention and the other active compound or compounds are formulated in a single pharmaceutical composition. Examples of compounds which may be included in pharmaceutical compositions with the compounds of the formula (1) are bronchodilators such as sympathomimetic amines for example isoprenaline, isoetharine, sulbutamol, phenylephrine and ephedrine or xanthine derivatives for example theophylline and aminophylline, anti-allergic agents for example disodium cromoglycate, histamine H_1-antagonists, vasodilators for example hydralazine, angiotensin converting enzyme inhibitors for example captopril, anti-anginal agents for example isosorbide nitrate, glyceryl trinitrate and pentaerythritol tetranitrate, anti-arrhythmic agents for example quinidine, procainamide and lignocaine, calcium antagonists for example verapamil and nifedipine, diuretics such as thiazides and related compounds for example bendrofluazide, chlorothiazide, chlorothalidone, hydrochlorothiazide, and other diuretics for example frusemide and triamterene, and sedatives for example nitrazepam, flurazepam and diazepam.

In another aspect the present invention provides a process for the preparation of compounds of the formula (1) or pharmaceutically acceptable salts thereof, which process comprises :

a) cyclising a compound of the formula (2) :

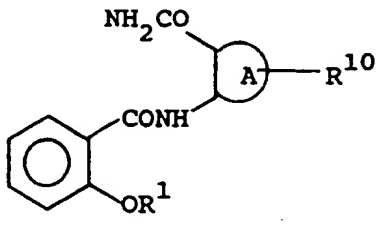


(2)

wherein L^1 is a displaceable group, R^1 and

are as hereinbefore defined, and R^{10} is a group R^2 as hereinbefore defined or a precursor thereof; or

b) cyclising a compound of the formula (3) :

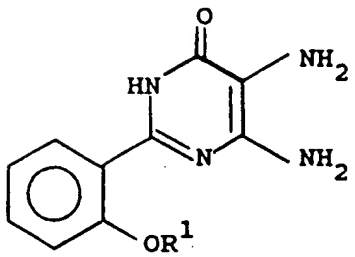


(3)

wherein R^1, R^{10} and

are as hereinbefore defined;

c) for compounds wherein R^2 and R are both hydrogen, reacting a compound of the formula (4) with glyoxal :



(4)

wherein R^1 is as hereinbefore defined;

d) for compounds wherein R^2 is 6-hydroxy and R is hydrogen, reacting a compound of the formula (4) as hereinbefore defined with chloral;

e) for compounds wherein R^2 and R are both hydroxy, reacting a compound of the formula (4) as hereinbefore defined with $(COL)_2$ wherein L is a leaving group;

and thereafter where necessary :

- converting a group R^{10} to a group R^2;
- optionally forming a pharmaceutically acceptable salt.

Suitably the cyclisation of a compound of the formula (2) is performed in the presence of a base such as an alkali metal carbonate or triethylamine, in an aprotic solvent such as dimethylformamide, acetonitrile or N-methylpyrrolidone, at ambient or an elevated temperature, for example 50-170 • C, conveniently at the reflux temperature of the reaction mixture. Suitably L^1 is halo for example bromo or chloro.

Suitably a compound of the formula (3) is cyclised by heating at an elevated temperature, for example 50-150 • C, in the presence of an acid or a base in a suitable solvent such as aqueous C -4alcohols, water, toluene, a halohydrocarbon or acetonitrile. Conveniently a compound of the formula (3) is cyclised by heating in pyridine or aqueous base such as sodium hydroxide at the reflux temperature of the reaction mixture.

Suitably an acid addition salt (e.g. the sulphate or chloride) of a compound of the formula (4) is reacted with glyoxal hydrate or with chloral hydrate in a suitable solvent such as water or C_{1-4}alkanols or mixtures thereof at an elevated temperature e.g. 40-150 • C, conveniently at the reflux temperature of the reaction mixture.

Suitably a compound of the formula (4) is reacted with $(COL)_2$ in a solvent such as a C_{1-4}alkanol or C_{1-4}alkoxyC_{1-4}alkanol or mixtures thereof at an elevated temperature e.g. 40-150 • C, conveniently at the reflux temperature of the reaction mixture. suitably L is C_{1-6}alkoxy such as methoxy or ethoxy or halo such as bromo or chloro.

Examples of R^{10} being a precursor to a group R^2 is when R^{10} is a halo or C_{1-6}alkylthio group. Such groups can be converted to a $-NR^4R^5$ group by reaction with an amine HNR^4R^5 in a suitable solvent such as a C_{1-4}-alkanol or pyridine at an elevated temperature, for example 50-120 • C, conveniently in a pressure vessel.

A compound of the formula (1) wherein R^2 is C_{1-6}alkylthio can suitably be converted to the corresponding compound wherein R^2 is C_{1-6}alkylsulphonyl by reaction with an oxidizing agent, for example with at least two equivalents of a peroxy acid such as m-chloroperoxybenzoic acid.

A compound of the formula (1) wherein R^2 is C_{1-6}alkylsulphonyl can suitably be converted to the corresponding compound wherein R^2 is $-NR^4R^5$ by reaction with an amine HNR^4R^5 in a suitable solvent such as a halohydrocarbon or toluene at ambient or elevated temperature for example 40-100 • C.

A compound of the formula (1) wherein R^2 is C_{1-6}alkylsulphonyl can suitably be converted to the corresponding compound wherein R^2 is C_{1-6}alkoxy by reaction with a C_{1-6}alkoxide, eg an alkali metal C_{1-6}alkoxide such as sodium methoxide or ethoxide, in a C_{1-6}alkanol at ambient or elevated temperature, for example 40-100 • C.

A compound of the formula (1) wherein R^2 is C_{1-6}-alkylthio can suitably be converted to the corresponding compound wherein R^2 is hydrazino by reaction with hydrazine.

A compound of the formula (1) wherein R^2 is hydrazino can be converted to the corresponding compound wherein R^2 is hydrogen by treatment with silver oxide.

A compound of the formula (1) wherein R^2 is C_{1-6}alkoxy can suitably be prepared by reacting a compound of the formula (1) wherein R^2 is C_{1-6}alkylthio with an alkali metal C_{1-6}alkoxide such as sodium methoxide or ethoxide.

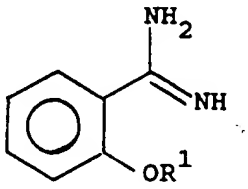
A compound of the formula (1) wherein R^2 is C_{1-6}alkoxy can be converted to the corresponding compound wherein R^2 is hydroxy by hydrolysis, for example by treatment with hydrochloric acid.

A compound of the formula (1) wherein R^2 is amino can suitably be converted to the corresponding compound where R^2 is -NHCOR^3 by reaction with a formylating or C_{2-7}alkanoylating agent. Examples of such reagents include formic acid, C_{1-6}alkyl formate, formamide, acetic anhydride, propionic anhydride or acetylchloride.

A compound of the formula (1) wherein R^4 R^5 is C_{1-6}alkyl substituted by C_{1-6}alkythio can suitably be converted to the corresponding compound wherein R^4 or R^5 is C_{1-6}alkyl substituted by C_{1-6}alkylsulphinyl by reaction with one equivalent of an oxidising agent such as a peroxy acid, for example m-chloroperoxybenzoic acid. The C_{1-6}alkylsulphinyl compound can similarly be oxidised to a compound of the formula (1) wherein R^4 or R^5 is C_{1-6}alkyl substituted by C_{1-6}alkylsulphonyl.

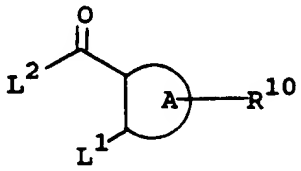
A compound of the formula (1) wherein R^4 or R^5 is C_{1-6}alkyl substituted by -CO_2R^7 in which R^7 is C_{1-6}alkyl can suitably be hydrolysed by reaction with aqueous base, for example aqueous sodium hydroxide to form the corresponding compound wherein R^7 is hydrogen.

The compounds of the formula (2) can be prepared by reaction of a compound of the formula (5) :



(5)

wherein R^1 is as hereinbefore defined, with a compound of the formula (6) :



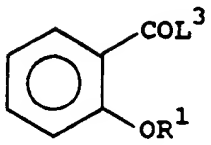
(6)

wherein L^2 is a leaving group and L^1, R^{10} and

are as hereinbefore defined.

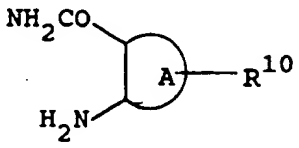
Suitably L^2 is C_{1-6}alkoxy or halo for example methoxy, ethoxy, chloro or bromo. Conveniently a solution of a compound of the formula (5) is initially formed by treatment of an acid addition salt of a compound of the formula (5) with a suitable base, for example triethylamine, a sodium alkoxide or sodium hydride, in an organic solvent such as a C_{1-4}alkanol, acetonitrile or dimethylformamide and the solution is then treated with a compound of the formula (6) at a moderate temperature for example 0-60 °C, conveniently ambient, to afford a compound of formula (2). Suitable acid addition salts are those formed with inorganic acids such as hydrochloric or sulphuric acid or with strong organic acids such as methanesulphonic or p-toluenesulphonic acid. Suitably a compound of the formula (2) is isolated and is then cyclised as hereinbefore described. Alternatively, a compound of the formula (2) is not isolated but is cyclised in situ by stirring at ambient or an elevated temperature, for example 40-170 °C.

A compound of the formula (3) can be prepared by reaction of a compound of the formula (7) :



(7)

wherein R^1 is as hereinbefore defined and L^3 is halo, with a compound of the formula (8):



(8)

wherein R^{10} and

are as hereinbefore defined.

Suitably L^3 is chloro or bromo. Suitably a compound of the formula (7) is reacted with a compound of the formula (8) at ambient or elevated temperature e.g. 50-100 °C in a suitable solvent such as toluene, acetonitrile or a halohydrocarbon e.g. chloroform or dichloromethane, optionally in the presence of a base such as pyridine or triethylamine, to form a compound of the formula (3) which may be cyclised in situ or may be isolated and thereafter cyclised as hereinbefore described.

The compounds of the formulae (4) and (5) and acid addition salts thereof are known or preparable in conventional manner from US Patent 3819631.

The compound of the formula (6), (7) and (8) are known or can be prepared by methods known in the art, for example in J. Org. Chem., 19, 1633, (1954); J. Org. Chem., 17, 542, (1952); J. Am. Chem. Soc., 78, 973, (1956); Chem. Ber., 96, 266, (1963); J. Chem. Soc. Perkin Trans. 1 (6), 1574 (1979); J. Org. Chem., 50, 2293-2298 (1985), J. Org. Chem., 37, 3958 (1972), J. Org. Chem., 34, 2102 (1969), Aust. J. Chem. 1974, 27, 1781-90, Aust. J. Chem. 1973, 26, 1689, and J. Heterocycl. Chem. 1968, 5, 581.

Pharmaceutically acceptable acid addition salts of the compounds of the formula (1) wherein R^2 is $-NR^4R^5$ or hydrazino may be prepared from the corresponding base of the compounds of the formula (1) in conventional manner. For example the base may be reacted with an acid in a C_{1-4}alkanol, or an ion-exchange resin may be used. The salts of the compounds of the formula (1) may be inter-converted using ion-exchange resins. Non-pharmaceutically acceptable salts are therefore of use as they can be converted to pharmaceutically acceptable salts.

Pharmaceutically acceptable base addition salts of the compounds of the formula (1) may be prepared by standard methods, for example by reacting a solution of the compound of the formula (1) with a solution of the base.

The following biological test methods, data and Examples serve to illustrate this invention.

Bronchodilatation - In vivo

Male guinea-pigs of the Dunkin Hartley strain (500 - 600g) were anaesthetised with Sagatal (pentobarbital sodium) (60 mg/kg). Airway resistance was measured using a modification of the classical Konzett-Rossler technique (J. Pharm. Methods, 13, 309-315, 1985). U46619 (9,11-methaneoepoxy-PGH_2) was infused i.v. at a rate of 2.5 nmol/min, this produced a steady state of bronchoconstriction (approximately 120% increase from basal airway resistance). The compound under test was administered by i.v. bolus injection, and the subsequent peak inhibition of bronchoconstriction recorded.

The dose of compound required to reduce the U46619-induced bronchoconstriction by 50% is given as the BD_{50}. The compounds of Examples 1, 2 and 9 had BD_{50} values in the range 2.8 - 4.9 μmol/kg. These results demonstrate in vivo antibronchoconstrictor activity.

Vasodilatation - In vivo

Male Wistar rats (300 g) were anaesthetised with a sodium 5-ethyl-5-(1-methylpropyl)-2-thiobarbiturate/sodium pentobarbitone mixture i.p. (62.5 and 22.5 mg/kg respectively). The trachea was cannulated and the rats breathed spontaneously air enriched with O_2 (5 ml/min). Blood pressure was recorded from a carotid artery and a jugular vein was cannulated for the adminstration of compounds. The temperature of the animal was maintained at 37 °C by the use of an electric blanket. The abdominal aorta was separated from the inferior vena cava, distal to the renal arteries and was cannulated centrally to supply the perfusion pump with blood and distally for the perfusion of the hind quarters at constant pressure. The perfusion circuit was primed with 5% bovine serum albumin dissolved in 0.9% sodium chloride solution, pH adjusted to 7.4. Initially the pump rate was set between 10 and 15 ml/min to match the hind quarter perfusion pressure to that of the systemic circulation. Once set, the pressure remained unaltered for the rest of the experiment. A change in the speed of the pump (equivalent to hindquarter blood flow) was used to assess the changes in hindquarter vascular resistance. All compounds were adminstered as a bolus i.v. The compound of Example 12 caused a 38% increase in hindquarter blood flow at a dose of 10 μmol/kg.

Anti-allergic activity

Male Duncan Hartley guinea-pigs (250-300 g) were sensitised to ovalbumen by i.p. injection of 2 ml of $50mg.ml^{-1}$ i.p. and 0.2 ml s.c. Three weeks later they were anaesthetised with $60mg.kg^{-1}$ sodium pentabarbitone. The trachea was cannulated and the animal respired at a rate of 40 breaths per minute and at an initial tracheal inflation pressure of 16 mmHg. Tracheal inflation pressure was measured by a transducer connected to a side arm of the respiration circuit. The carotid artery was cannulated for the measurement of blood pressure and the signal was used to trigger an instantaneous rate meter. A jugular vein was cannulated for the administration of drug and allergen. After surgery the animals were allowed to stabilise and the drug was administered i.v. as a bolus. Following this, ovalbumen $1mg.kg^{-1}$ was injected i.v. as the antigen challenge either 2, 15 or 30 minutes following drug treatment and the peak bronchoconstrictor response recorded. For the control group ovalbumen only was given. One ovalbumen challenge per guinea-pig was used and n = 6 for each time point. The percentage increase in tracheal inflation pressure was calculated. The following results indicating an anti-allergic activity were obtained.

Compound of Example	Dose μmol/kg	% Inhibition of Control Bronchoconstrictor Response 30 min after drug administration
1	28	9

Phosphodiesterase activity

The activity of the compounds of the present invention as inhibitors of a calmodulin insensitive cyclic GMP phosphodiesterase was measured using the procedure described in European Patent Application No. 293063. The compounds of Examples 1-4, 6, 7, 10, 11 and 13-20 had IC_{50} values (the concentration of inhibitor required for 50% inhibition of enzyme activity) in the range 0.55 to 11.38 μM. The compounds of the present invention have the advantage that they are selective in not inhibiting cyclic AMP phosphodiesterase (type III).

Example 1

2-(2-Propoxyphenyl)pyrido[2,3-d]pyrimid-4(3H)-one

a) A solution of 2-propoxybenzoyl chloride (0.99 g) in acetonitrile (7.5 ml) was added dropwise over 5 minutes to a cooled (0 °C), stirred mixture of 2-aminonicotinamide (0.69 g) and triethylamine (0.51 g) in acetonitrile (7.5 ml). The reaction mixture was stirred at ambient temperature for 1.5 hours, allowed to stand overnight and then evaporated under reduced pressure to dryness. The residue was washed with

water to afford a solid (1.63 g) which was twice recrystallised from methanol to afford 2-(2-propoxybenzamido)nicotinamide, 0.92 g, m.p. 181-184 °C.

b) A stirred mixture of 2-(2-propoxybenzamido)nicotinamide (0.77 g) and pyridine (0.8 ml) in 2 Normal sodium hydroxide (20 ml) was heated under reflux for 30 minutes. The cooled reaction mixture was neutralised with 2 Normal hydrochloric acid to afford a precipitate which together with another precipitate similarly prepared from 2-(2-propoxybenzamido)nicotinamide (0.1 g) was recrystallised from ethanol-ether to afford white needles (0.65 g) which were washed with water to afford the title compound, 0.55 g. m.p. 110-111 °C.

Example 2

2-(2-Propoxyphenyl)pyrido[3,4-d]pyrimid-4(3H)-one

a) In a similar manner to Example 1 a) reaction of 2-propoxybenzoyl chloride (0.99 g), 3-aminoisonicotinamide (0.69 g) and triethylamine (0.51 g) in acetonitrile (15 ml) afforded a crude product (1.45 g) which was recrystallised from methanol to afford 3-(2-propoxybenzamido)isonicotinamide, 0.73 g, m.p. 214-7 °C.

b) In a similar manner to Example 1 b) cyclisation of 3-(2-propoxybenzamido)isonicotinamide (0.72 g) afforded a crude product which was recrystallised from ethanol-water to afford the title compound 0 44 g, m.p. 181-183 °C.

Example 3

2-(2-Propoxyphenyl)pyrido[4,3-d]pyrimid-4(3H)-one

a) In a similar manner to Example 1 a) reaction of 2-propoxybenzoyl chloride (0.79 g), 4-aminonicotinamide (0.55 g) and triethylamine (0.40 g) in acetonitrile (12 ml) afforded a crude product which was recrystallised from ethanol-ether to afford 4-(2-propoxybenzamido)nicotinamide, 0.53 g, m.p. 164-166 °C.

b) In a similar manner to Example 1 b) cyclisation of 4-(2-propoxybenzamido)nicotinamide (0.52 g) afforded a crude product which was recrystallised from ethanol-water to afford the title compound, 0.45 g, m.p. 135-136 °C.

Example 4

2-(2-Propoxyphenyl)pyrido[3,2-d]pyrimid-4(3H)-one

a) In a similar manner to Example 1 a) reaction of 2-propoxybenzoyl chloride (0.99 g), 3-aminopicolinamide (0.69 g) and triethylamine (0.51 g) in acetonitrile (15 ml) afforded a crude product which was recrystallised from methanol to afford 3-(2-propoxybenzamido) picolinamide, 0.91 g, m.p. 116-118 °C.

b) In a similar manner to Example 1 b) cyclisation of 3-(2-propoxybenzamido)picolinamide (0.90 g) afforded a crude product which was recrystallised from ethanol-water to afford the title compound, 0,28 g, m.p. 126-127 °C.

The mother liquor was evaporated under reduced pressure to dryness and the residue recrystallised from ethanol-water to afford a further sample of the title compound, 0.46 g, m.p. 125-126.5 °C.

Example 5

2-(2-Propoxyphenyl)pteridin-4(3H)-one

A stirred mixture of 4,5-diamino-2-(2-propoxyphenyl)pyrimidin-6-one sulphate (1.25 g), glyoxal hydrate (0.4 g), water (62.5 ml) and n-butanol (1 ml) was heated under reflux for one hour to afford a crude product (0.97 g) which was collected and washed with water. The crude product together with another sample (0.12 g) similarly prepared was eluted from a silica column with chloroform. The combined fractions containing product were evaporated under reduced pressure to afford a solid (0.96 g) which was recrystallised from ethanol-water to afford the title compound, 0.8 g, m.p. 177.5-178.5 °C.

Example 6

2-(2-Propoxyphenyl)pteridin-4,6(3H,5H)-dione

A solution of chloral hydrate (1.74 g) in 50% aqueous methanol (10 ml) was added over 10 minutes to a stirred solution of 4,5-diamino-2-(2-propoxyphenyl)pyrimidin-6-one sulphate (1.89 g) in 50% aqueous methanol (60 ml) at 80 °C and the reaction mixture was stirred at 80 °C for 1.5 hours. The cooled reaction mixture was filtered to remove an orange brown solid which was discarded. On standing overnight the filtrate afforded a crude solid product (0.96 g) which was collected and washed with dilute aqueous potassium bicarbonate and water. The crude product together with another sample (0.20 g) similarly prepared was eluted from a silica column with chloroform. The combined fractions containing product were evaporated under reduced pressure to afford a solid (0.54 g) which was recrystallised from acetonitrile to afford the title compound, 0.39 g, m.p. 232-233.5 °C.

Example 7

2-(2-Propoxyphenyl)pteridin-4,6,7(3H,5H,8H)-trione

A stirred mixture of 4,5-diamino-2-(2-propoxyphenyl)pyrimidin-6-one sulphate (1.0 g), triethylamine (0.42 ml) and diethyl oxalate (1.2 ml) in methoxyethanol (10 ml) was heated under reflux for 7 hours. The reaction mixture was stirred overnight at ambient temperature and a precipitate was collected and washed with water and ethanol to afford a crude product (0.70 g, m.p. 312-315 °C). The crude product together with another sample (0.34 g) similarly prepared was twice recrystallised from dimethylformamide to afford the title compound, 0.40 g, m.p. 320-321 °C.

Example 8

5,6-Dihydro-3-methylthio-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine

a) A filtered solution of 2-propoxybenzamidine in ethanol (prepared from sodium, 0.28 g, in ethanol, 50 ml, and 2-propoxybenzamidine hydrochloride, 2.63 g) was added to a stirred, cooled solution of ethyl 3-chloro-6-methylthio-1,2,4-triazine-5-carboxylate (2.6 g) in ethanol (50 ml). After one hour the temperature was allowed to rise to ambient, stirred for a further one hour, then filtered to give 6-chloro-3-methylthio-5-(2-propoxybenzamidinocarbonyl)-1,2,4-triazine, 3.45 g, m.p. 229-230 °C.

b) A stirred mixture of the product from (a) above 3.45 g), potassium carbonate (1.3 g) and dimethylformamide (200 ml) was heated at 150 °C for 6.5 hours. Potassium carbonate (1.3 g) was added and the mixture was heated for a further 2 hours. Water (150 ml) was added to the residue left after evaporation, and the mixture was acidified with acetic acid to give 5,6-dihydro-3-methylthio-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4] triazine, 2.88 g, m.p. 195-197 °C. Recrystallisation from ethanol gave the pure product m.p. 224-225 °C.

Example 9

3-Amino-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine

5,6-Dihydro-3-methylthio-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine (0.7 g) was heated for 30 hours with ethanolic ammonia (50 ml) at 100 °C in a pressure vessel. The cooled mixture was filtered to give the crude product (0.21 g) which was recrystallised from ethanol to give the pure title compound, m.p. 322-325 °C.

Example 10

3-Methylamino-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine

5,6-Dihydro-3-methylthio-5-oxo-7-(2-propoxyphenyl)-pyrimido[5,4-e][1,2,4]triazine (340 mg) was treated with a solution of methylamine in industrial methylated spirit (33%, 15 ml) at 70 °C in a pressure vessel (172 kPa) for 10 hours. The cooled reaction mixture was evaporated under reduced pressure to afford a yellow solid (290 mg) which was recrystallised from ethanol and then acetonitrile to afford the title

compound, 120 mg, m.p. decomposes over 260 °C.

Example 11

3-Methoxy-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine

A stirred mixture of 5,6-dihydro-3-methylthio-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine (0.80 g) and sodium methoxide (prepared from sodium, 0.28 g and methanol) in methanol (50 ml) was heated under reflux for 1.5 hours. The cooled reaction mixture was neutralised by the addition of glacial acetic acid (0.7 ml) to afford a yellow precipitate (0.63 g) which was recrystallised from methanol to afford the title compound, 0.47 g, m.p. 221-222 °C.

Example 12

3-Methylthio-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine

A solution of 2-propoxybenzamidine (from 2.9 g of the hydrochloride) in 2-propanol (50 ml) was added at 2 °C to a solution of 3-methylthio-5-chloro-6-carboethoxy-1,2,4-triazine (2.08 g) in 2-propanol (100 ml). The mixture was stirred at 2 °C for 2 hours, allowed to stand at room temperature overnight, and then heated under reflux for 3 hours. The residue left after evaporation was dissolved in chloroform and the solution was washed with dilute hydrochloric acid. Evaporation of the chloroform and treatment of the residue with ethanol gave a solid (0.2 g) which was recrystallised from ethanol to give 3-methylthio-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine, 0.12 g, m.p. 247-249 °C.

Example 13

3-Amino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine

In a similar manner to that described in Example 10, 3-methylthio-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine (1.42 g) was reacted with ethanolic ammonia (70 ml) for 20 hours to give the crude title compound, (0.80 g) which together with another sample (0.17 g), similarly prepared, was recrystallised from ethanol to afford the title compound, 0.54 g, m.p. 255-256 °C.

Example 14

3-Methylamino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine

3-Methylthio-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine (2.0 g) was treated with a solution of methylamine in industrial methylated spirit (33%, 30 ml) at 75 °C in a pressure vessel for 20 hours. The cooled reaction mixture was evaporated under reduced pressure to afford an oily solid which was dissolved in chloroform. The organic solution was washed with water, dried and evaporated under reduced pressure to afford a yellow oily solid which was eluted from a silica column with chloroform/methanol (5%). The fractions containing product were combined and evaporated under reduced pressure to afford a yellow solid (180 mg) which together with another sample (50 mg), similarly prepared, was recrystallised from ethanol to afford the title compound, 140 mg, m.p. 261-263 °C.

Example 15

3-Methoxy-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine

In a similar manner to Example 11, 3-methylthio-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e]-[1,2,4] triazine (0.5 g) was treated for 3 hours with sodium methoxide (prepared from sodium, 0.17 g, and methanol) to afford the title compound, 0.34 g, m.p. 234-235 °C (recrystallised from methanol).

Exampl 16

3,8-Di xo-6-(2-propoxyphenyl)-3,4,7,8-t trahydropyrimido[4,5-e][1,2,4]triazine

A stirred mixture of 3-methylthio-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine (0.5 g) and sodium methoxide (prepared from sodium, 0.17 g, and methanol) in methanol (50 ml) was heated under reflux for 3 hours. The cooled reaction mixture was evaporated under reduced pressure to afford a yellow solid which was dissolved in water and acidified with 2 Normal hydrochloric acid to yield a yellow solid (420 mg) which was recrystallised from dimethylformamide to afford the title compound, 0.16 g, m.p. 298-299 • C.

Example 17

3-Dimethylamino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine

3-Methylthio-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine (0.6 g) was treated with a solution of dimethylamine in industrial methylated spirit (33%, 20 ml) at 100 • C in a pressure vessel for 24 hours. The cooled reaction mixture was evaporated under reduced pressure to afford a yellow solid residue which was dissolved in dilute aqueous sodium hydroxide and filtered. The filtrate was acidified with a few drops of concentrated hydrochloric acid to afford a yellow precipitate which was collected, washed with water and recrystallised from methanol to afford the title compound, 0.44 g, m.p. 257.5-259 • C.

Example 18

3-Methylthio-8-oxo-6-(2-allyloxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine

A cooled (5 • C) solution of 3-methylthio-5-chloro-6-carboethoxy-1,2,4-triazine (prepared by heating 3-methylthio-5-oxo-6-carboethoxy-4,5-dihydro-1,2,4-triazine, 1.5 g, with thionyl chloride, 30 ml, under reflux for two hours and thereafter removing thionyl chloride) in acetonitrile (30 ml) was added to a cooled stirred mixture of 2-allyloxybenzamidine hydrochloride (2.23 g) and triethylamine (1.06 g) in acetonitrile (50 ml). The mixture was stirred with cooling (0-5 • C) for 15 minutes, then more triethylamine (0.71 g) was added and the reaction mixture was stirred at ambient temperature for two hours and left standing overnight. A yellow precipitate was collected, washed with water and recrystallised from acetonitrile and then from acetonitrile/ethanol (50%) to afford the title compound, 0.35 g, m.p. 238-239 • C.

Example 19

3-Methylthio-8-oxo-6-(2-isobutoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine

In a similar manner to Example 18 reaction of 3-methylthio-5-chloro-6-carboethoxy-1,2,4-triazine (prepared from 3-methylthio-5-oxo-6-carboethoxy-4,5-dihydro-1,2,4-triazine, 1.5 g) with 2-isobutoxybenzamidine hydrochloride (2.37 g) and triethylamine (1.75 g) afforded the crude title compound (1.71 g). This was recrystallised from acetonitrile, then dissolved in chloroform, the organic solution was washed with 2 Normal hydrochloric acid (x 2), chloroform removed under reduced pressure and the residue recrystallised twice from ethanol to afford the title compound, 0.32 g, m.p. 237-238 • C.

Example 20

3-Methylthio-8-oxo-6-(2-cyclopropylmethoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine

In a similar manner to Example 18 reaction of 3-methylthio-5-chloro-6-carboethoxy-1,2,4-triazine (prepared from 3-methylthio-5-oxo-6-carboethoxy-4,5-dihydro-1,2,4-triazine, 1.5 g) with 2-cyclopropoxybenzamidine hydrochloride (2.35 g) and triethylamine (1.75 g) afforded a yellow solid (1.31 g) which was recrystallised from acetonitrile and then from acetonitrile/ethanol (50%) to afford the title compound, 0.70 g, m.p. 235-236 • C.

Example 21

3-M thylthio-8-oxo-6-(2-methoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine

A cooled (0 • C) solution of 2-methoxybenzamidine (from 1.97 g of the hydrochloride) in acetonitrile (17 ml) was added to a cooled solution of 3-methylthio-5-chloro-6-carboethoxy-1,2,4-triazine (prepared from 3-methylthio-5-oxo-6-carboethoxy-4,5-dihydro-1,2,4-triazine, 1.08 g, and thionyl chloride, 20 ml) in acetonitrile (17 ml). Triethylamine (0.51 g) was added and the reaction mixture was stirred with cooling (0 • C) for one hour and then at ambient temperature for 17 hours to afford a yellow solid which was washed with acetonitrile and ether to afford the crude title compound (1.39 g). A sample (0.35 g) of this was washed twice with boiling methanol to afford the title compound, 0.25 g, m.p. 267.5-268.5 • C. The remaining material (1.04 g) was similarly treated with boiling methanol to afford the title compound, 0.91 g, m.p. 266-268 • C.

Example 22

Pharmaceutical compositions for oral administration are prepared by combining the following :

	% w/w		
2-(2-Propoxyphenyl)pyrido-[2,3-d]pyrimid-4(3H)-one	0.5	3.0	7.14
2% w/w Soya lecithin in soya bean oil	90.45	88.2	84.41
Hydrogenated vegetable shortening and beeswax	9.05	8.8	8.45

The formulations are then filled into individual soft gelatin capsules.

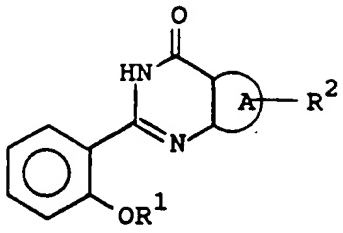
Example 23

A pharmaceutical composition for parenteral adminstration is prepared by dissolving the title compound of Example 9 (0.02 g) in polyethylene glycol 300 (25 ml) with heating. This solution is then diluted with water for injections Ph. Eur. (to 100 ml). The solution is then sterilised by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

Claims

Claims for the following Contracting States: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

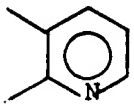
1. A compound of the formula (1):



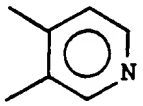
(1)

or a pharmaceutically acceptable salt thereof, wherein

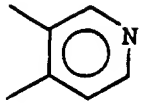
is a ring of sub-formula (a), (b), (c), (d), (e), (f) or (g):



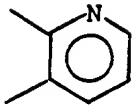
(a)



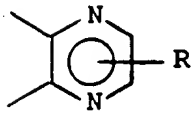
(b)



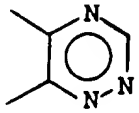
(c)



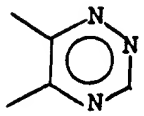
(d)



(e)



(f)



(g),

R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-6}alkyl, or C_{1-6}alkyl substituted by 1 to 6 fluoro groups;

R^2 is C_{1-6}alkylthio, C_{1-6}alkylsulphonyl, C_{1-6}alkoxy, hydroxy, hydrogen, hydrazino, C_{1-6}alkyl, phenyl, $-NHCOR^3$ wherein R^3 is hydrogen or C_{1-6}alkyl, or $-NR^4R^5$ wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring, or R^4 and R^5 are independently hydrogen, C_{3-5}cycloalkyl or C_{1-6}alkyl which is optionally substituted by $-CF_3$, phenyl, $-S(O)_nC_{1-6}$alkyl wherein n is 0, 1 or 2, $-OR^6$, $-CO_2R^7$ or $-NR^8R^9$ wherein R^6 to R^9 are independently hydrogen or C_{1-6}alkyl, provided that the carbon atom adjacent to the nitrogen atom is not substituted by said $-S(O)_nC_{1-6}$alkyl, $-OR^6$ or $-NR^8R^9$ groups; and

R is hydrogen and can also be hydroxy when R^2 is hydroxy.

2. A compound according to claim 1 wherein R^1 is C_{2-5}alkyl.

3. A compound acording to claim 1 wherein R^1 is n-propyl.

4. A compound according to any one of claims 1 to 3 wherein R^2 is C_{1-6}alkylthio, C_{1-6}alkylsulphonyl or C_{1-6}alkoxy.

5. A compound according to any one of claims 1 to 3 wherein R^2 is hydrogen, hydroxy or hydrazino.

6. A compound according to any one of claims 1 to 3 wherein R^2 is phenyl or C_{1-6}alkyl.

7. A compound according to any one of claims 1 to 3 wherein R^2 is -NHCOR^3 or -NR^{4}R^5.

8. A compound according to any one of claims 1 to 7 wherein

is a group of sub-formula (a).

9. A compound according to any one of claims 1 to 7 wherein

is a group of sub-formula (b).

10. A compound according to any one of claims 1 to 7 wherein

is a group of sub-formula (c).

11. A compound according to any one of claims 1 to 7 wherein

is a group of sub-formula (d).

12. A compound according to any one of claims 1 to 7 wherein

is a group of sub-formula (e).

13. A compound according to any one of claims 1 to 7 wherein

is a group of sub-formula (f).

14. A compound according to any one of claims 1 to 7 wherein

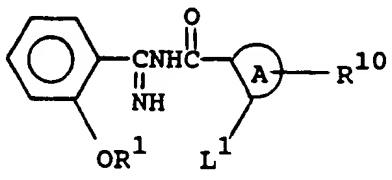
is a group of sub-formula (g).

15. A compound according to claim 1 which is :
2-(2-propoxyphenyl)pyrido[2,3-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pyrido[3,4-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pyrido[4,3-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pyrido[3,2-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pteridin-4(3H)-one,
2-(2-propoxyphenyl)pteridin-4,6(3H,5H)-dione,
2-(2-propoxyphenyl)pteridin-4,6,7(3H,5H,8H)-trione,
5,6-dihydro-3-methylthio-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e] [1,2,4]triazine,
3-amino-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine,
3-methylamino-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine,
3-methoxy-5,6-dihydro-5-oxo-7-)2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine,
3-methylthio-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-amino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methylamino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methoxy-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3,8-dioxo-6-(2-propoxyphenyl)-3,4,7,8-tetrahydropyrimido[4,5-e][1,2,4]triazine,
3-dimethylamino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methylthio-8-oxo-6-(2-allyloxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methylthio-8-oxo-6-(2-isobutoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methylthio-8-oxo-6-(2-cyclopropylmethoxyphenyl)-7,8dihydropyrimido[4,5-e][1,2,4]triazine or
3-methylthio-8-oxo-6-(2-methoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine
or a pharmaceutically acceptable salt thereof.

16. A compound according to any one of claims 1 to 15 for use as a medicament.

17. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 15 and a pharmaceutically acceptable carrier.

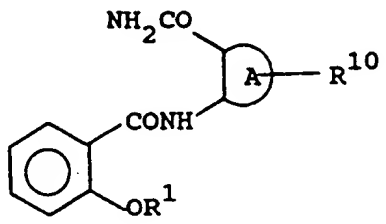
18. A process for preparing a compound of the formula (1) or a pharmaceutically acceptable salt thereof as defined in claim 1 which comprises :
a) cyclising a compound of the formula (2) :



(2)

wherein L^1 is a displaceable group, R^1 and

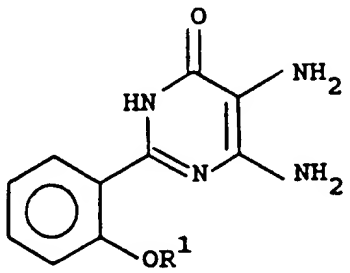
are as defined in claim 1, and R^{10} is a group R^2 as defined in claim 1 or a precursor thereof; or
b) cyclising a compound of the formula (3) :



(3)

wherein R^1, R^{10} and

are as hereinbefore defined;
c) for compounds wherein R^2 and R are both hydrogen, reacting a compound of the formula (4) with glyoxal :

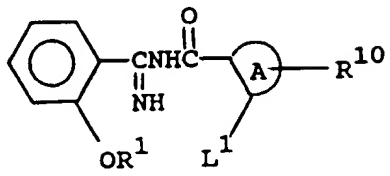


(4)

wherein R^1 is as hereinbefore defined;
d) for compounds wherein R^2 is 6-hydroxy and R is hydrogen, reacting a compound of the formula (4) as hereinbefore defined with chloral;
e) for compounds wherein R^2 and R are both hydroxy, reacting a compound of the formula (4) as hereinbefore defined with $(COL)_2$ wherein L is a leaving group;
and thereafter where necessary :

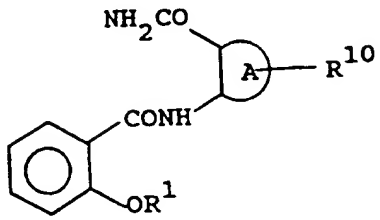
- converting a group R^{10} to a group R^2;
- optionally forming a pharmaceutically acceptable salt.

19. A compound of the formula (2) as defined in claim 18:



(2)

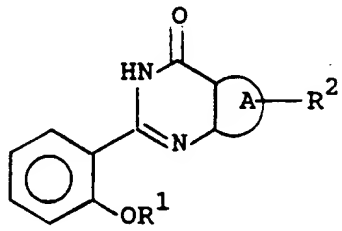
20. A compound of the formula (3) as defined in claim 18.



(3)

Claims for the following Contracting State: ES

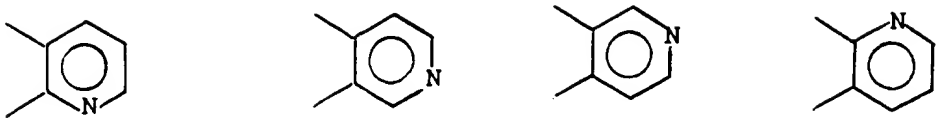
1. A process for preparing a compound of the formula (1) :



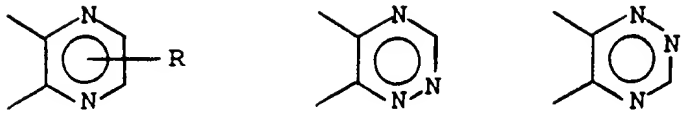
(1)

or a pharmaceutically acceptable salt thereof, wherein

is a ring of sub-formula (a), (b), (c), (d), (e), (f) or (g) :



(a) (b) (c) (d)



(e) (f) (g),

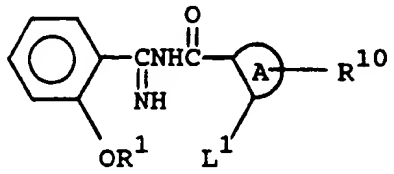
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-6}alkyl, or C_{1-6}alkyl substituted by 1 to 6 or fluoro groups;

R^2 is C_{1-6}alkylthio, C_{1-6}alkylsulphonyl, C_{1-6}alkoxy, hydroxy, hydrogen, hydrazino, C_{1-6}alkyl, phenyl, $-NHCOR^3$ wherein R^3 is hydrogen or C_{1-6}alkyl, or $-NR^4R^5$, wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring, or R^4 and R^5 are independently hydrogen, C_{3-5}cycloalkyl or C_{1-6}alkyl which is optionally substituted by $-CF_3$, phenyl, $-S(O)_nC_{1-6}$alkyl wherein n is 0, 1 or 2, $-OR^6$, $-CO_2R^7$ or $-NR^8R^9$ wherein R^6 to R^9 are independently hydrogen or C_{1-6}alkyl, provided that the carbon atom adjacent to the nitrogen atom is not substituted by said $-S(O)_nC_{1-6}$alkyl, $-OR^6$ or $-NR^8R^9$ groups; and

R is hydrogen and can also be hydroxy when R^2 is hydroxy;

which process comprises:

a) cyclising a compound of the formula (2) :

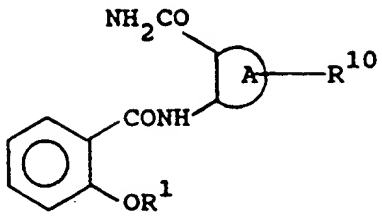


(2)

wherein L^1 is a displaceable group, R^1 and

are as hereinbefore defined and R^{10} is a group R^2 as hereinbefore defined or a precursor thereof; or

b) cyclising a compound of the formula (3) :

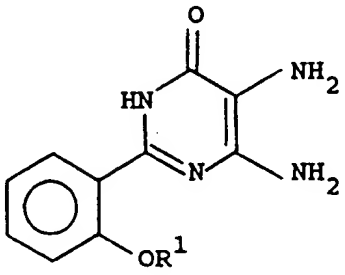


(3)

wherein R^1, R^{10} and

are as hereinbefore defined;

c) for compounds wherein R^2 and R are both hydrogen, reacting a compound of the formula (4) with glyoxal :



(4)

wherein R^1 is as hereinbefore defined;

d) for compounds wherein R^2 is 6-hydroxy and R is hydrogen, reacting a compound of the formula (4) as hereinbefore defined with chloral;

e) for compounds wherein R^2 and R are both hydroxy, reacting a compound of the formula (4) as hereinbefore defined with $(COL)_2$ wherein L is a leaving group;

and thereafter where necessary :

- converting a group R^{10} to a group R^2;
- optionally forming a pharmaceutically acceptable salt.

2. A process according to claim 1 for preparing a compound wherein R^1 is C_{2-5}alkyl.

3. A process according to claim 1 for preparing a compound wherein R^1 is n-propyl.

4. A process according to any one of claims 1 to 3 for preparing a compound wherein R^2 is C_{1-6}alkylthio, C_{1-6}alkylsulphonyl or C_{1-6}alkoxy.

5. A process according to any one of claims 1 to 3 for preparing a compound wherein R^2 is hydrogen, hydroxy or hydrazino.

6. A process according to any one of claims 1 to 3 for preparing a compound wherein R^2 is phenyl or C_{1-6}alkyl.

7. A process according to any one of claims 1 to 3 for preparing a compound wherein R^2 is -NHCOR^3 or -NR^{4}R^5.

8. A process according to any one of claims 1 to 7 for preparing a compound wherein

is a group of sub-formula (a).

9. A process according to any one of claims 1 to 7 for preparing a compound wherein

is a group of sub-formula (b).

10. A process according to any one of claims 1 to 7 for preparing a compound wherein

is a group of sub-formula (c).

11. A process according to any one of claims 1 to 7 for preparing a compound wherein

is a group of sub-formula (d).

12. A process according to any one of claims 1 to 7 for preparing a compound wherein

is a group of sub-formula (e).

13. A process according to any one of claims 1 to 7 for preparing a compound wherein

is a group of sub-formula (f).

14. A process according to any one of claims 1 to 7 for preparing a compound wherein

is a group of sub-formula (g).

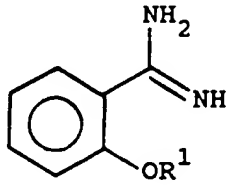
15. A process according to claim 1 for preparing a compound which is:
2-(2-propoxyphenyl)pyrido[2,3-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pyrido[3,4-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pyrido[4,3-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pyrido[3,2-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pteridin-4(3H)-one,
2-(2-propoxyphenyl)pteridin-4,6(3H,5H)-dione,
2-(2-propoxyphenyl)pteridin-4,6,7(3H,5H,8H)-trione,
5,6-dihydro-3-methylthio-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine,
3-amino-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine,
3-methylamino-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine,
3-methoxy-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine,
3-methylthio-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-amino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methylamino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methoxy-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3,8-dioxo-6-(2-propoxyphenyl)-3,4,7,8-tetrahydropyrimido[4,5-e][1,2,4]triazine,
3-dimethylamino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methylthio-8-oxo-6-(2-allyloxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methylthio-8-oxo-6-(2-isobutoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methylthio-8-oxo-6-(2-cyclopropylmethoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine or
3-methylthio-8-oxo-6-(2-methoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine
or a pharmaceutically acceptable salt thereof.

16. A process according to claim 1 wherein L^1 is halo.

17. A process according to claim 1 wherein L is C_{1-6} alkoxy or halo.

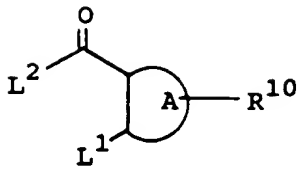
18. A process for preparing a pharmaceutical composition which comprises bringing into association a compound of the formula (1) as defined in any one of claims 1 to 15 and a pharmaceutically acceptable carrier.

19. A process for preparing a compound of the formula (2) as defined in claim 1 which comprises reacting a compound of the formula (5) :



(5)

wherein R^1 is as defined in claim 1,
with a compound of the formula (6) :

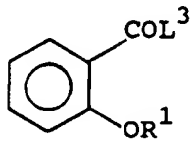


(6)

wherein L^2 is a leaving group and $L1^1$, R^{10} and

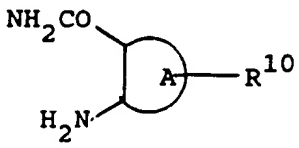
are as defined in claim 1.

20. A process for preparing a compound of the formula (3) as defined in claim 1 which comprises reacting a compound of the formula (7) :



(7)

wherein R^1 is as defined in claim 1 and L^3 is halo, with a compound of the formula (8) :



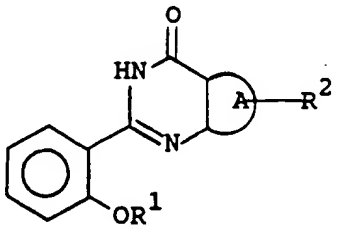
(8)

wherein R^{10} and

are as defined in claim 1.

Claims for the following Contracting State: GR

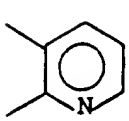
1. A process for preparing a compound of the formula (1) :



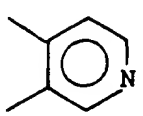
(1)

or a pharmaceutically acceptable salt thereof, wherein

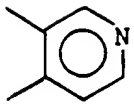
is a ring of sub-formula (a), (b), (c), (d), (e), (f) or (g) :



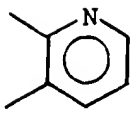
(a)



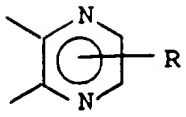
(b)



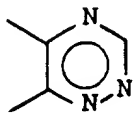
(c)



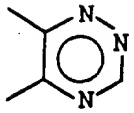
(d)



(e)



(f)



(g),

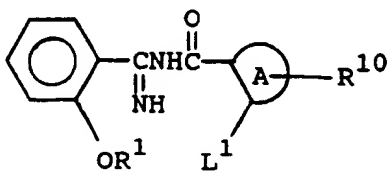
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-6}alkyl, or C_{1-6}alkyl substituted by 1 to 6 fluoro groups;

R^2 is C_{1-6}alkylthio, C_{1-6}alkylsulphonyl, C_{1-6}alkoxy, hydroxy, hydrogen, hydrazino, C_{1-6}alkyl, phenyl, $-NHCOR^3$ wherein R^3 is hydrogen or C_{1-6}alkyl, or $-NR^4R^5$, wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring, or R^4 and R^5 are independently hydrogen, C_{3-5}cycloalkyl or C_{1-6}alkyl which is optionally substituted by $-CF_3$, phenyl, $-S(O)_nC_{1-6}$alkyl wherein n is 0, 1 or 2, $-OR^6$, $-CO_2R^7$ or $-NR^8R^9$ wherein R^6 to R^9 are independently hydrogen or C_{1-6}alkyl, provided that the carbon atom adjacent to the nitrogen atom is not substituted by said $-S(O)_nC_{1-6}$alkyl, $-OR^6$ or $-NR^8R^9$ groups; and

R is hydrogen and can also be hydroxy when R^2 is hydroxy;

which process comprises:

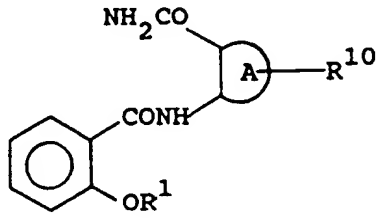
a) cyclising a compound of the formula (2) :



(2)

wherein L^1 is a displaceable group, R^1 and

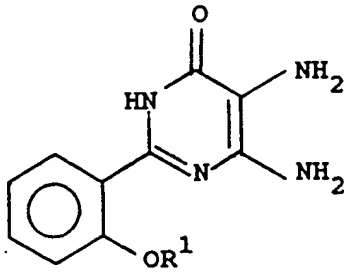
are as hereinbefore defined and R^{10} is a group R^2 as hereinbefore defined or a precursor thereof; or
b) cyclising a compound of the formula (3) :



(3)

wherein R^1, R^{10} and

are as hereinbefore defined;
c) for compounds wherein R^2 and R are both hydrogen, reacting a compound of the formula (4) with glyoxal :



(4)

wherein R^1 is as hereinbefore defined;
d) for compounds wherein R^2 is 6-hydroxy and R is hydrogen, reacting a compound of the formula (4) as hereinbefore defined with chloral;
e) for compounds wherein R^2 and R are both hydroxy, reacting a compound of the formula (4) as hereinbefore defined with $(COL)_2$ wherein L is a leaving group;
and thereafter where necessary :

- converting a group R^{10} to a group R^2;
- optionally forming a pharmaceutically acceptable salt.

2. A process according to claim 1 for preparing a compound wherein R^1 is C_{2-5}alkyl.

3. A process according to claim 1 for preparing a compound wherein R^1 is n-propyl.

4. A process according to any one of claims 1 to 3 for preparing a compound wherein R^2 is C_{1-6}alkylthio, C_{1-6}alkylsulphonyl or C_{1-6}alkoxy.

5. A process according to any one of claims 1 to 3 for preparing a compound wherein R^2 is hydrogen, hydroxy or hydrazino.

6. A process according to any one of claims 1 to 3 for preparing a compound wherein R^2 is phenyl or C_{1-6} alkyl.

7. A process according to any one of claims 1 to 3 for preparing a compound wherein R^2 is $-NHCOR^3$ or $-NR^4R^5$.

8. A process according to any one of claims 1 to 7 for preparing a compound wherein

is a group of sub-formula (a).

9. A process according to any one of claims 1 to 7 for preparing a compound wherein

is a group of sub-formula (b).

10. A process according to any one of claims 1 to 7 for preparing a compound wherein

is a group of sub-formula (c).

11. A process according to any one of claims 1 to 7 for preparing a compound wherein

is a group of sub-formula (d).

12. A process according to any one of claims 1 to 7 for preparing a compound wherein

is a group of sub-formula (e).

13. a process according to any one of claims 1 to 7 for preparing a compound wherein

is a group of sub-formula (f).

14. A process according to any one of claims 1 to 7 for preparing a compound wherein

is a group of sub-formula (g).

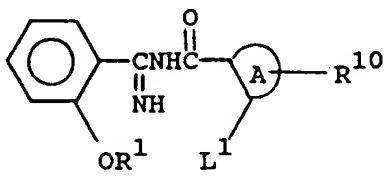
15. A process according to claim 1 for preparing a compound which is :
2-(2-propoxypenyl)pyrido[2,3-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pyrido[3,4-d]pyrimid-4-(3H)-one,
2-(2-propoxyphenyl)pyrido[4,3-d]pyrimid-4-(3H)-one,
2-(2-propoxyphenyl)pyrido[3,2-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pteridin-4(3H)-one,
2-(2-propoxyphenyl)pteridin-4,6(3H,5H)-dione,
2-(2-propoxyphenyl)pteridin-4,6,7(3H,5H,8H)-trione,
5,6-dihydro-3-methylthio-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine,
3-amino-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine,
3-methylamino-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine,
3-methoxy-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine,
3-methylthio-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-amino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methylamino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methoxy-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3,8-dioxo-6-(2-propoxyphenyl)-3,4,7,8-tetrahydropyrimido[4,5-e][1,2,4]triazine,
3-dimethylamino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methylthio-8-oxo-6-(2-allyloxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methylthio-8-oxo-6-(2-isobutoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4)triazine,
3-methylthio-8-oxo-6-(2-cyclopropylmethoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine or
3-methylthio-8-oxo-6-(2-methoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine
or a pharmaceutically acceptable salt thereof.

16. A process according to claim 1 wherein L^1 is halo.

17. A process according to claim 1 wherein L is C_{1-6} alkoxy or halo.

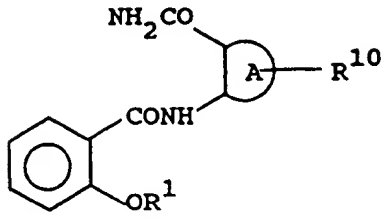
18. A process for preparing a pharmaceutical composition which comprises bringing into association a compound of the formula (1) as defined in any one of claims 1 to 15 and a pharmaceutically acceptable carrier.

19. A compound of the formula (2) as defined in claim 1:



(2)

20. A compound of the formula (3) as defined in claim 1:

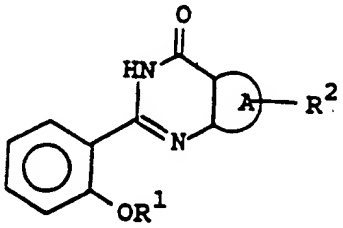


(3)

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

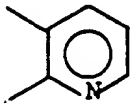
1. Verbindung der Formel (1)



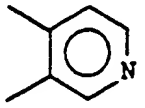
(1)

oder ein pharmazeutisch verträgliches Salz davon, wobei

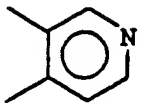
ein Ring der Unterformel (a), (b), (c), (d), (e), (f) oder (g) ist



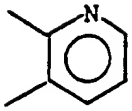
(a)



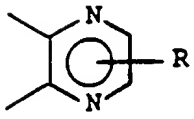
(b)



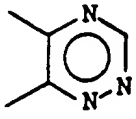
(c)



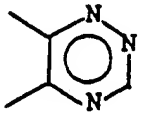
(d)



(e)



(f)



(g),

R^1 ein C_{1-6}-Alkyl-, C_{2-6}Alkenyl-, C_{3-5}-Cycloalkyl-C_{1-6}-alkyl-, oder ein mit 1 bis 6 Fluoratomen

substituierter C_{1-6}-Alkylrest ist;
R^2 ein C_{1-6}-Alkylthio-, C_{1-6}-Alkylsulfonyl-, C_{1-6}-Alkoxyrest, eine Hydroxylgruppe, ein Wasserstoffatom, eine Hydrazingruppe, ein C_{1-6}-Alkylrest, eine Phenylgruppe, ein -NHCOR^3-Rest, wobei R^3 ein Wasserstoffatom oder ein C_{1-6}-Alkylrest ist, oder ein -NR^{4}R^5-Rest ist, wobei R^4 und R^5 zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen Pyrrolidin-, Piperidin-, Hexahydroazepin-, Morpholin- oder einen Piperazinring bilden, oder R^4 und R^5 unabhängig voneinander Wasserstoffatome, C_{3-5}-Cycloalkylreste oder gegebenenfalls mit $-CF_3$, Phenyl, $-S(O)_nC_{1-6}$-Alkyl, wobei n den Wert 0, 1 oder 2 hat, $-OR^6$, $-CO_2R^7$ oder -NR^{8}R^9 substituierte C_{1-6}-Alkylreste sind, wobei R^6 bis R^9 unabhängig voneinander Wasserstoffatome oder C_{1-6}-Alkylreste sind, mit der Maßgabe, daß das dem Stickstoffatom benachbarte Kohlenstoffatom nicht mit dem den $-S(O)_nC_{1-6}$-Alkyl, $-OR^6$- oder -NR^{8}R^9-Rest substituiert ist, und
R ein Wasserstoffatom ist, oder eine Hydroxylgruppe sein kann, wenn R^2 eine Hydroxylgruppe ist.

2. Verbindung nach Anspruch 1, wobei R^1 ein C_{2-5}-Alkylrest ist.

3. Verbindung nach Anspruch 1, wobei R^1 eine n-Propylgruppe ist.

4. Verbindung nach einem der Ansprüche 1 bis 3, wobei R^2 ein C_{1-6}-Alkylthio-, C_{1-6}-Alkylsulfonyl- oder C_{1-6}-Alkoxyrest ist.

5. Verbindung nach einem der Ansprüche 1 bis 3, wobei R^2 ein Wasserstoffatom, eine Hydroxyl- oder eine Hydrazingruppe ist.

6. Verbindung nach einem der Ansprüche 1 bis 3, wobei R^2 eine Phenylgruppe oder ein C_{1-6}-Alkylrest ist.

7. Verbindung nach einem der Ansprüche 1 bis 3, wobei R^2 ein -NHCOR^3- oder -NR^{4}R^5- Rest ist.

8. Verbindung nach einem der Ansprüche 1 bis 7, wobei

ein Rest der Unterformel (a) ist.

9. Verbindung nach einem der Ansprüche 1 bis 7, wobei

ein Rest der Unterformel (b) ist.

10. Verbindung nach einem der Ansprüche 1 bis 7, wobei

ein Rest der Unterformel (c) ist.

11. Verbindung nach einem der Ansprüche 1 bis 7, wobei

ein Rest der Unterformel (d) ist.

12. Verbindung nach einem der Ansprüche 1 bis 7, wobei

ein Rest der Unterformel (e) ist.

13. Verbindung nach einem der Ansprüche 1 bis 7, wobei

ein Rest der Unterformel (f) ist.

14. Verbindung nach einem der Ansprüche 1 bis 7, wobei

ein Rest der Unterformel (g) ist.

15. Verbindung nach Anspruch 1, die
2-(2-Propoxyphenyl)pyrido[2,3-d]pyrimid-4(3H)-on,
2-(2-Propoxyphenyl)pyrido[3,4-d]pyrimid-4(3H)-on,
2-(2-Propoxyphenyl)pyrido[4,3-d]pyrimid-4(3H)-on,
2-(2-Propoxyphenyl)pyrido[3,2-d]pyrimid-4(3H)-on,
2-(2-Propoxyphenyl)pteridin-4(3H)-on,
2-(2-Propoxyphenyl)pteridin-4,6(3H,5H)-dion,
2-(2-Propoxyphenyl)pteridin-4,6,7(3H,5H,8H)-trion,
5,6-Dihydro-3-methylthio-5-oxo-7-(2-propoxyphenyl)-pyrimido[5,4-e][1,2,4]triazin,
3-Amino-5,6-Dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazin,
3-Methylamino-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)-pyrimido[5,4-e][1,2,4]triazin,
3-Methoxy-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4e][1,2,4]triazin,
3-Methylthio-8-oxo-6-(2-propoxyphenyl)-7,8-dihydro-pyrimido[4,5-e][1,2,4]triazin,
3-Amino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazin,
3-Methylamino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydro-pyrimido[4,5-e][1,2,4]triazin,
3-Methoxy-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazin,
3,8-Dioxo-6-(2-propoxyphenyl)-3,4,7,8-tetrahydropyrimido-[4,5-e][1,2,4]triazin,
3-Dimethylamino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazin,
3-Methylthio-8-oxo-6-(2-allyloxyphenyl)-7,8-dihydro-pyrimido[4,5-e][1,2,4]triazin,
3-Methylthio-8-oxo-6-(2-isobutoxyphenyl)-7,8-dihydrorimido[4,5-e][1,2,4]triazin,
3-Methylthio-8-oxo-6-(2-cyclopropylmethoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazin, oder
3-Methylthio-8-oxo-6-(2-methoxyphenyl)-7,8-dihydro-pyri mido[4,5-e][1,2,4]triazin,

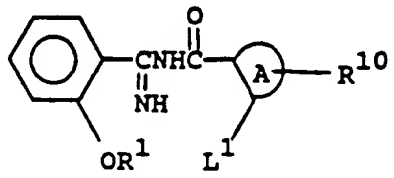
oder ein pharmazeutisch verträgliches Salz davon ist.

16. Verbindung nach einem der Ansprüche 1 bis 15 zur Verwendung als Arzneistoff.

17. Arzneimittel, umfassend eine Verbindung nach einem der Ansprüche 1 bis 15 und einen pharmazeutisch verträglichen Träger.

18. Verfahren zur Herstellung einer Verbindung der Formel (1) oder eines pharmazeutisch verträglichen Salzes davon wie in Anspruch 1 definiert, umfassend:

a) Cyclisieren einer Verbindung der Formel (2)

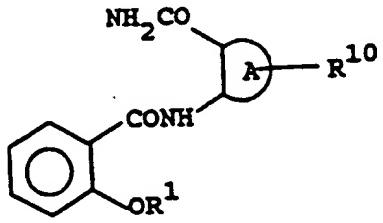


(2)

wobei L^1 eine ersetzbare Gruppe ist, R^1 und

wie in Anspruch 1 definiert sind und R^{10} ein Rest R^2 wie in Anspruch 1 definiert oder ein Vorläufer davon ist; oder

b) Cyclisieren einer Verbindung der Formel (3)

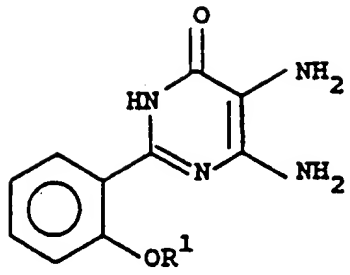


(3)

wobei R^1, R^{10} und

wie vorstehend definiert sind;

c) für Verbindungen, in denen R^2 und R beide Wasserstoffatome sind, Umsetzen einer Verbindung der Formel (4) mit Glyoxal:



(4)

wobei R^1 wie vorstehend definiert ist;

d) für Verbindungen, in denen R^2 eine 6-Hydroxylgruppe und R ein Wasserstoffatom ist, Umsetzen einer Verbindung der Formel (4) wie vorstehend definiert mit Chloral,

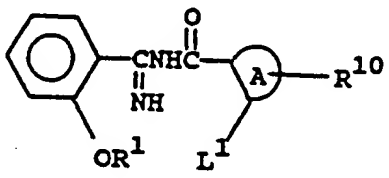
e) für Verbindungen, in denen R^2 und R beide Hydroxylgruppen sind, Umsetzen einer Verbindung der Formel (4) wie vorstehend definiert mit $(COL)_2$, wobei L eine Abgangsgruppe ist;

und anschließend, falls notwendig:

Umwandeln eines Restes R^{10} in einen Rest R^2,

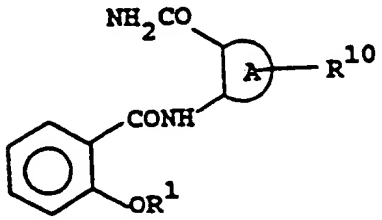
gegebenenfalls Erzeugen eines pharmazeutisch verträglichen Salzes.

19. Verbindung der Formel (2) wie in Anspruch 18 definiert:



(2)

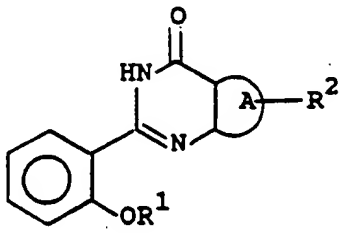
20. Verbindung der Formel (3) wie in Anspruch 18 definiert



(3)

Patentansprüche für folgenden Vertragsstaat : ES

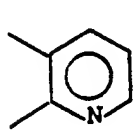
1. Verfahren zur Herstellung einer Verbindung der Formel (1)



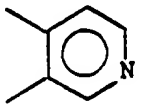
(1)

oder eines pharmazeutisch verträglichen Salzes davon, wobei

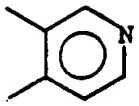
ein Ring der Unterformel (a), (b), (c), (d), (e), (f) oder (g) ist



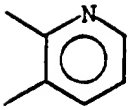
(a)



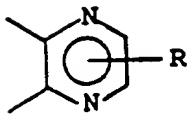
(b)



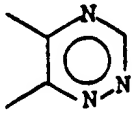
(c)



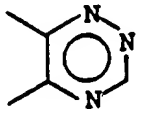
(d)



(e)



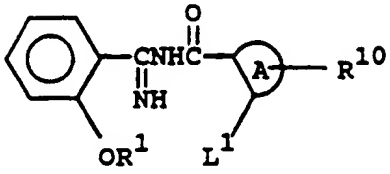
(f)



(g),

R^1 ein C_{1-6}-Alkyl-, C_{2-6}Alkenyl-, C_{3-5}-Cycloalkyl-C_{1-6}-alkyl-, oder ein mit 1 bis 6 Fluoratomen substituierter C_{1-6}-Alkylrest ist;
R^2 ein C_{1-6}-Alkylthio-, C_{1-6}-Alkylsulfonyl-, C_{1-6}-Alkoxyrest, eine Hydroxylgruppe, ein Wasserstoffatom, eine Hydrazingruppe, ein C_{1-6}-Alkylrest, eine Phenylgruppe, ein -$NHCOR^3$-Rest, wobei R^3 ein Wasserstoffatom oder ein C_{1-6}-Alkylrest ist, oder ein -NR^4R^5-Rest ist, wobei R^4 und R^5 zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen Pyrrolidin-, Piperidin-, Hexahydroazepin-, Morpholin- oder Piperazinring bilden, oder R^4 und R^5 unabhängig voneinander Wasserstoffatome, C_{3-5}-Cycloalkylreste oder gegebenenfalls mit $-CF_3$, Phenyl, -$S(O)_nC_{1-6}$-Alkyl, wobei n den Wert 0, 1 oder 2 hat, -OR^6, -CO_2R^7 oder -NR^8R^9 substituierte C_{1-6}-Alkylreste sind, wobei R^6 bis R^9 unabhängig voneinander Wasserstoffatome oder C_{1-6}-Alkylreste sind, mit der Maßgabe, daß das dem Stickstoffatom benachbarte Kohlenstoffatom nicht mit dem -$S(O)_nC_{1-6}$-Alkyl-, -OR^6- oder -NR^8R^9-Resten substituiert ist, und
R ein Wasserstoffatom ist, oder eine Hydroxylgruppe sein kann, wenn R^2 eine Hydroxylgruppe ist, umfassend

a) Cyclisieren einer Verbindung der Formel (2)

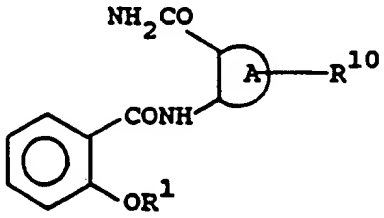


(2)

wobei L^1 eine ersetzbare Gruppe ist, R^1 und

wie in Anspruch 1 definiert sind und R^{10} ein Rest R^2 wie in Anspruch 1 definiert oder ein Vorläufer davon ist; oder

b) Cyclisieren einer Verbindung der Formel (3)

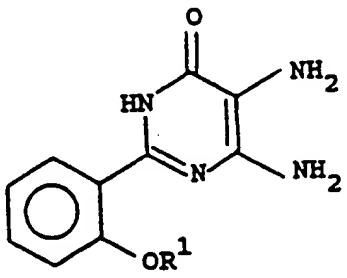


(3)

wobei R^1, R^{10} und

wie vorstehend definiert sind;

c) für Verbindungen, in denen R^2 und R beide Wasserstoffatome sind, Umsetzen einer Verbindung der Formel (4) mit Glyoxal:



(4)

wobei R^1 wie vorstehend definiert ist;

d) für Verbindungen, in denen R^2 eine 6-Hydroxylgruppe und R ein Wasserstoffatom ist, Umsetzen einer Verbindung der Formel (4) wie vorstehend definiert mit Chloral,

e) für Verbindungen, in denen R^2 und R beide Hydroxylgruppen sind, Umsetzen einer Verbindung der Formel (4) wie vorstehend definiert mit $(COL)_2$, wobei L eine Abgangsgruppe ist;
und anschließend, falls notwendig:
Umwandeln eines Restes R^{10} in einen Rest R^2,
gegebenenfalls Erzeugen eines pharmazeutisch verträglichen Salzes.

2. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung, bei der R^1 ein C_{2-5}-Alkylrest ist.

3. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung, bei der R^1 eine n-Propylgruppe ist.

4. Verfahren nach einem der Ansprüche 1 bis 3 zur Herstellung einer Verbindung, bei der R^2 ein C_{1-6}-Alkylthio-, C_{1-6}-Alkylsulfonyl- oder ein C_{1-6}-Alkoxyrest ist.

5. Verfahren nach einem der Ansprüche 1 bis 3 zur Herstellung einer Verbindung, bei der R^2 ein Wasserstoffatom, eine Hydroxyl- oder eine Hydrazingruppe ist.

6. Verfahren nach einem der Ansprüche 1 bis 3 zur Herstellung einer Verbindung, bei der R^2 eine Phenylgruppe oder ein C_{1-6}-Alkylrest ist.

7. Verfahren nach einem der Ansprüche 1 bis 3 zur Herstellung einer Verbindung, bei der R^2 ein $-NHCOR^3$- oder $-NR^4R^5$- Rest ist.

8. Verfahren nach einem der Ansprüche 1 bis 7 zur Herstellung einer Verbindung, bei der

ein Rest der Unterformel (a) ist.

9. Verfahren nach einem der Ansprüche 1 bis 7 zur Herstellung einer Verbindung, bei der

ein Rest der Unterformel (b) ist.

10. Verfahren nach einem der Ansprüche 1 bis 7 zur Herstellung einer Verbindung, bei der

ein Rest der Unterformel (c) ist.

11. Verfahren nach einem der Ansprüche 1 bis 7 zur Herstellung einer Verbindung, bei der

ein Rest der Unterformel (d) ist.

12. Verfahren nach einem der Ansprüche 1 bis 7 zur Herstellung einer Verbindung, bei der

ein Rest der Unterformel (e) ist.

13. Verfahren nach einem der Ansprüche 1 bis 7 zur Herstellung einer Verbindung, bei der

ein Rest der Unterformel (f) ist.

14. Verfahren nach einem der Ansprüche 1 bis 7 zur Herstellung einer Verbindung, bei der

ein Rest der Unterformel (g) ist.

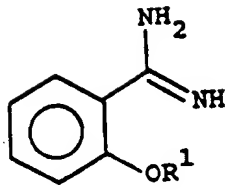
15. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung, nämlich:
2-(2-Propoxyphenyl)pyrido[2,3-d]pyrimid-4(3H)-on,
2-(2-Propoxyphenyl)pyrido[3,4-d]pyrimid-4(3H)-on,
2-(2-Propoxyphenyl)pyrido[4,3-d]pyrimid-4(3H)-on,
2-(2-Propoxyphenyl)pyrido[3,2-d]pyrimid-4(3H)-on,
2-(2-Propoxyphenyl)pteridin-4(3H)-on,
2-(2-Propoxyphenyl)pteridin-4,6(3H,5H)-dion,
2-(2-Propoxyphenyl)pteridin-4,6,7(3H,5H,8H)-trion,
5,6-Dihydro-3-methylthio-5-oxo-7-(2-propoxyphenyl)-pyrimido[5,4-e][1,2,4]triazin,
3-Amino-5,6-Dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e)[1,2,4]triazin,
3-Methylamino-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)-pyrimido[5,4-e][1,2,4]triazin,
3-Methoxy-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4e][1,2,4]triazin,
3-Methylthio-8-oxo-6-(2-propoxyphenyl)-7,8-dihydro-pyrimido[4,5-e][1,2,4]triazin,
3-Amino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazin,
3-Methylamino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydro-pyrimido[4,5-e][1,2,4]triazin,
3-Methoxy-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazin,
3,8-Dioxo-6-(2-propoxyphenyl)-3,4,7,8-tetrahydropyrimido-[4,5-e][1,2,4]triazin,
3-Dimethylamino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazin,
3-Methylthio-8-oxo-6-(2-allyloxyphenyl)-7,8-dihydro-pyrimido[4,5-e][1,2,4]triazin,
3-Methylthio-8-oxo-6-(2-isobutoxyphenyl)-7,8-dihydro-pyrimido[4,5-e][1,2,4]triazin,
3-Methylthio-8-oxo-6-(2-cyclopropylmethoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazin, oder
3-Methylthio-8-oxo-6-(2-methoxyphenyl)-7,8-dihydro-pyrimido[4,5-e][1,2,4]triazin,
oder eines pharmazeutisch verträglichen Salzes davon.

16. Verfahren nach Anspruch 1, wobei L^1 ein Halogenatom ist.

17. Verfahren nach Anspruch 1, wobei L ein C_{1-6}-Alkoxyrest oder ein Halogenatom ist.

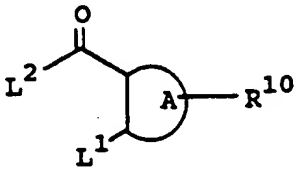
18. Verfahren zur Herstellung eines Arzneimittels, umfassend das Inverbindungbringen einer Verbindung der Formel (1), die wie in einem der Ansprüche 1 bis 15 definiert ist, mit einem pharmazeutisch vertraglichen Träger.

19. Verfahren zur Herstellung einer Verbindung der Formel (2) die wie in Anspruch 1 definiert ist, umfassend das Umsetzen einer Verbindung der Formel (5)



(5)

wobei R^1 wie in Anspruch 1 definiert ist mit einer Verbindung der Formel (6)

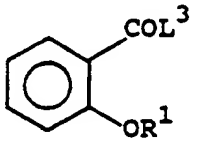


(6)

wobei L^2 eine Abgangsgruppe ist und L^1, R^{10} und

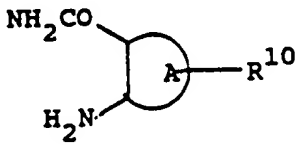
wie in Anspruch 1 definiert sind.

20. Verfahren zur Herstellung einer Verbindung der Formel (3) die wie in Anspruch 1 definiert ist, umfassend das Umsetzen einer Verbindung der Formel (7)



(7)

wobei R^1 wie in Anspruch 1 definiert ist und L^3 ein Halogenatom ist, mit einer Verbindung der Formel (8)



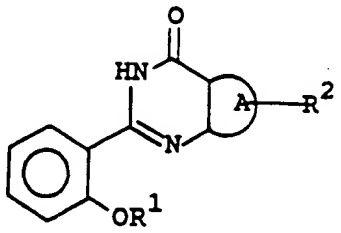
(8)

wobei R^{10} und

wie in Anspruch 1 definiert sind.

Patentansprüche für folgenden Vertragsstaat : GR

1. Verfahren zur Herstellung einer Verbindung der Formel (1)

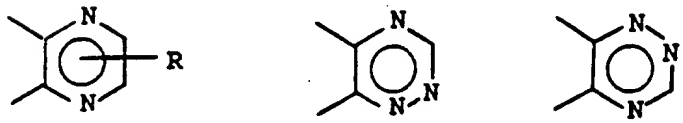


(1)

oder eines pharmazeutisch verträglichen Salzes davon, wobei

ein Ring der Unterformel (a), (b), (c), (d), (e), (f) oder (g) ist

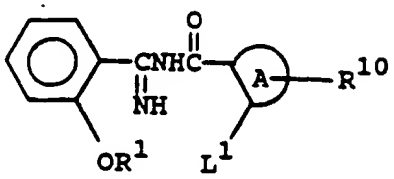
(a) (b) (c) (d)



(e) (f) (g),

R^1 ein C_{1-6}-Alkyl-, C_{2-6}Alkenyl-, C_{3-5}-Cycloalkyl-C_{1-6}-alkyl-, oder ein mit 1 bis 6 Fluoratomen substituierter C_{1-6}-Alkylrest ist;
R^2 ein C_{1-6}-Alkylthio-, C_{1-6}-Alkylsulfonyl, C_{1-6}-Alkoxyrest, eine Hydroxylgruppe, ein Wasserstoffatom, eine Hydrazingruppe, ein C_{1-6}-Alkylrest, eine Phenylgruppe, ein -NHCOR^3-Rest, wobei R^3 ein Wasserstoffatom oder ein C_{1-6}-Alkylrest ist, oder ein -NR^{4}R^5-Rest ist, wobei R^4 und R^5 zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen Pyrrolidin-, Piperidin-, Hexahydroazepin-, Morpholin- oder Piperazinring bilden, oder R^4 und R^5 unabhängig voneinander Wasserstoffatome, C_{3-5} Cycloalkylreste oder gegebenenfalls mit -CF_3, Phenyl, -S(O)$_n$C$_{1-6}$-Alkyl, wobei n den Wert 0, 1 oder 2 hat, -OR^6, -CO_2R^7 oder -NR^{8}R^9 substituierte C_{1-6}-Alkylreste sind, wobei R^6 bis R^9 unabhängig voneinander Wasserstoffatome oder C_{1-6}-Alkylreste sind, mit der Maßgabe, daß das dem Stickstoffatom benachbarte Kohlenstoffatom nicht mit dem -S(O)$_n$C$_{1-6}$-Alkyl, -OR^6- oder -NR^{8}R^9-Resten substituiert ist, und
R ein Wasserstoffatom ist, oder eine Hydroxylgruppe sein kann, wenn R^2 eine Hydroxylgruppe ist, umfassend

a) Cyclisieren einer Verbindung der Formel (2)

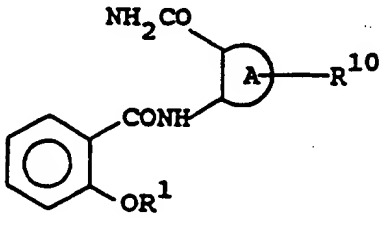


(2)

wobei L^1 eine ersetzbare Gruppe ist, R^1 und

wie in Anspruch 1 definiert sind und R^{10} ein Rest R^2 wie in Anspruch 1 definiert oder ein Vorläufer davon ist; oder

b) Cyclisieren einer Verbindung der Formel (3)

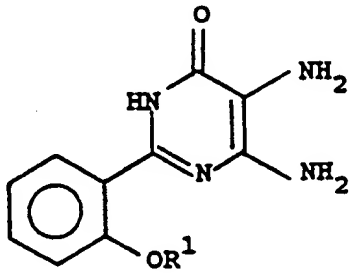


(3)

wobei R^1, R^{10} und

wie vorstehend definiert sind;

c) für Verbindungen, in denen R^2 und R beide Wasserstoffatome sind, Umsetzen einer Verbindung der Formel (4) mit Glyoxal:



(4)

wobei R^1 wie vorstehend definiert ist;

d) für Verbindungen, in denen R^2 eine 6-Hydroxylgruppe und R ein Wasserstoffatom ist, Umsetzen einer Verbindung der Formel (4) wie vorstehend definiert mit Chloral,

e) für Verbindungen, in denen R^2 und R beide Hydroxylgruppen sind, Umsetzen einer Verbindung der Formel (4) wie vorstehend definiert mit $(COL)_2$, wobei L eine Abgangsgruppe ist;

und anschließend, falls notwendig:
Umwandeln eines Restes R^{10} in einen Rest R^2,
gegebenenfalls Erzeugen eines pharmazeutisch verträglichen Salzes.

2. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung, bei der R^1 ein C_{2-5}-Alkylrest ist.

3. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung, bei der R^1 eine n-Propylgruppe ist.

4. Verfahren nach einem der Ansprüche 1 bis 3 zur Herstellung einer Verbindung, bei der R^2 ein C_{1-6}-Alkylthio-, C_{1-6}-Alkylsulfonyl- oder ein C_{1-6}-Alkoxyrest ist.

5. Verfahren nach einem der Ansprüche 1 bis 3 zur Herstellung einer Verbindung, bei der R^2 ein Wasserstoffatom, eine Hydroxyl- oder eine Hydrazingruppe ist.

6. Verfahren nach einem der Ansprüche 1 bis 3 zur Herstellung einer Verbindung, bei der R^2 eine Phenylgruppe oder ein C_{1-6}-Alkylrest ist.

7. Verfahren nach einem der Ansprüche 1 bis 3 zur Herstellung einer Verbindung, bei der R^2 ein $-NHCOR^3-$ oder $-NR^4R^5-$ Rest ist.

8. Verfahren nach einem der Ansprüche 1 bis 7 zur Herstellung einer Verbindung, bei der

ein Rest der Unterformel (a) ist.

9. Verfahren nach einem der Ansprüche 1 bis 7 zur Herstellung einer Verbindung, bei der

ein Rest der Unterformel (b) ist.

10. Verfahren nach einem der Ansprüche 1 bis 7 zur Herstellung einer Verbindung, bei der

ein Rest der Unterformel (c) ist.

11. Verfahren nach einem der Ansprüche 1 bis 7 zur Herstellung einer Verbindung, bei der

ein Rest der Unterformel (d) ist.

12. Verfahren nach einem der Ansprüche 1 bis 7 zur Herstellung einer Verbindung, bei der

ein Rest der Unterformel (e) ist.

13. Verfahren nach einem der Ansprüche 1 bis 7 zur Herstellung einer Verbindung, bei der

ein Rest der Unterformel (f) ist.

14. Verfahren nach einem der Ansprüche 1 bis 7 zur Herstellung einer Verbindung, bei der

ein Rest der Unterformel (g) ist.

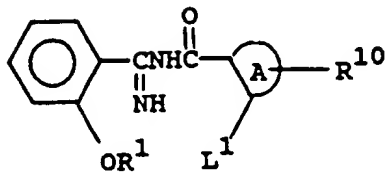
15. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung, nämlich:
2-(2-Propoxyphenyl)pyrido[2,3-d]pyrimid-4(3H)-on,
2-(2-Propoxyphenyl)pyrido[3,4-d]pyrimid-4(3H)-on,
2-(2-Propoxyphenyl)pyrido[4,3-d]pyrimid-4(3H)-on,
2-(2-Propoxyphenyl)pyrido[3,2-d]pyrimid-4(3H)-on,
2-(2-Propoxyphenyl)pteridin-4(3H)-on,
2-(2-Propoxyphenyl)pteridin-4,6(3H,5H)-dion,
2-(2-Propoxyphenyl)pteridin-4,6,7(3H,5H,8H)-trion,
5, 6-Dihydro-3-methylthio-5-oxo-7-(2-propoxyphenyl)-pyrimido[5,4-e][1,2,4]triazin,
3-Amino-5,6-Dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazin,
3-Methylamino-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)-pyrimido[5,4-e][1,2,4]triazin,
3-Methoxy-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4e][1,2,4]triazin,
3-Methylthio-8-oxo-6-(2-propoxyphenyl)-7,8-dihydro-pyrimido[4,5-e][1,2,4]triazin,
3-Amino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazin,
3-Methylamino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydro-pyrimido[4,5-e][1,2,4]triazin,
3-Methoxy-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazin,
3,8-Dioxo-6-(2-propoxyphenyl)-3,4,7,8-tetrahydropyrimido-[4,5-e][1,2,4]triazin,
3-Dimethylamino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazin,
3-Methylthio-8-oxo-6-(2-allyloxyphenyl)-7,8-dihydro-pyrimido[4,5-e][1,2,4]triazin,
3-Methylthio-8-oxo-6-(2-isobutoxyphenyl)-7,8-dihydro-pyrimido[4,5-e][1,2,4)triazin,
3-Methylthio-8-oxo-6-(2-cyclopropylmethoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4)triazin, oder
3-Methylthio-8-oxo-6-(2-methoxyphenyl)-7,8-dihydro-pyrimido[4,5-e][1,2,4]triazin,
oder eines pharmazeutisch verträglichen Salzes davon.

16. Verfahren nach Anspruch 1, wobei L^1 ein Halogenatom ist.

17. Verfahren nach Anspruch 1, wobei L ein C_{1-6}-Alkoxyrest oder ein Halogenatom ist.

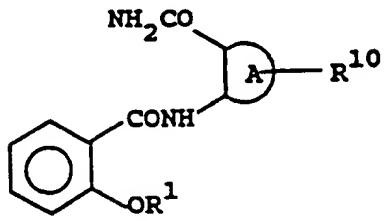
18. Verfahren zur Herstellung eines Arzneimittels, umfassend das Inverbindungbringen einer Verbindung der Formel (1), die wie in einem der Ansprüche 1 bis 15 definiert ist, mit einem pharmazeutisch verträglichen Träger.

19. Verbindung der Formel (2) wie in Anspruch 1 definiert:



(2)

20. Verbindung der Formel (3) wie in Anspruch 1 definiert:

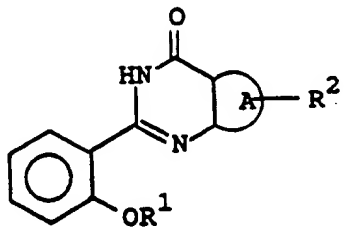


(3)

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

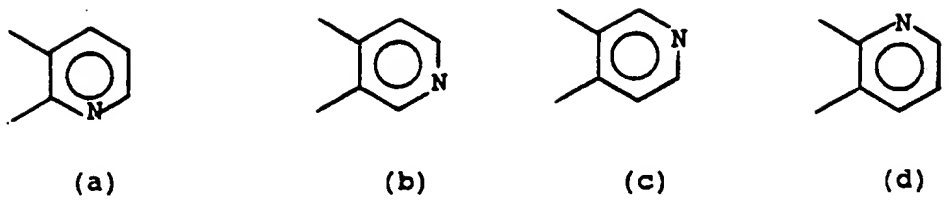
1. Composé de formule (1) :



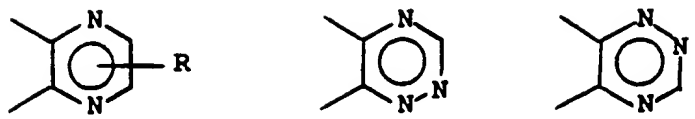
(1)

ou sel de celui-ci acceptable du point de vue pharmaceutique, dans laquelle :

est un noyau représenté par les sous-formules (a), (b), (c), (d), (e), (f) ou (g) :



(a) (b) (c) (d)



(e) (f) (g),

R^1 est un groupe alkyle en C_{1-6}, alcényle en C_{2-6}, cycloalkyl(en C_{3-5})-alkyle en C_{1-6} ou alkyle en C_{1-6} substitué par 1 à 6 atomes de fluor;

R^2 est un groupe alkylthio en C_{1-6}, alkylsulfonyle en C_{1-6}, alcoxy en C_{1-6}, hydroxy, atome d'hydrogène, groupe hydrazino, alkyle en C_{1-6}, phényle, $-NHCOR^3$ dans lequel R^3 est un atome d'hydrogène ou un groupe alkyle en C_{1-6}, ou $-NR^4R^5$, dans lequel R^4 et R^5 forment avec l'atome d'azote auquel ils sont attachés un groupe pyrrolidino, pipéridino, hexahydroazépino, morpholino ou pipérazino; ou bien R^4 et R^5 sont indépendamment un atome d'hydrogène, un groupe cycloalkyle en C_{3-5} ou alkyle en C_{1-6} qui est éventuellement substitué par $-CF_3$, phényle, $-S(O)_n$-alkyle en C_{1-6} dans lequel n est 0, 1 ou 2, $-OR^6$, $-CO_2R^7$ ou $-NR^8R^9$ dans lesquels R^6 à R^9 sont indépendamment un atome d'hydrogène ou un groupe alkyle en C_{1-6}, à condition que l'atome de carbone adjacent à l'atome d'azote ne soit pas substitué par ces groupes $-S(O)_n$-alkyle en C_{1-6}, $-OR^6$ ou $-NR^8R^9$; et

R est un atome d'hydrogène et peut aussi être un groupe hydroxy lorsque R^2 est un groupe hydroxy.

2. Composé suivant la revendication 1, dans lequel R^1 est un groupe alkyle en $_{2-5}$.

3. Composé suivant la revendication 1, dans lequel R^1 est un groupe n-propyle.

4. Composé suivant l'une quelconque des revendications 1 à 3, dans lequel R^2 est un groupe alkylthio en C_{1-6}, alkylsulfonyle en C_{1-6} ou alcoxy en C_{1-6}.

5. Composé suivant l'une quelconque des revendications 1 à 3, dans lequel R^2 est un atome d'hydrogène, un groupe hydroxy ou hydrazino.

6. Composé suivant l'une quelconque des revendications 1 à 3, dans lequel R^2 est un groupe phényle ou alkyle en C_{1-6}.

7. Composé suivant l'une quelconque des revendications 1 à 3, dans lequel R^2 est un groupe $-NHCOR^3$ ou $-NR^4R^5$.

8. Composé suivant l'une quelconque des revendications 1 à 7, dans lequel

est un groupe de sous-formule (a).

9. Composé suivant l'une quelconque des revendications 1 à 7, dans lequel,

est un groupe de sous-formule (b).

10. Composé suivant l'une quelconque des revendications 1 à 7, dans lequel

est un groupe de sous-formule (c).

11. Composé suivant l'une quelconque des revendications 1 à 7, dans lequel

est un groupe de sous-formule (d).

12. Composé suivant l'une quelconque des revendications 1 à 7, dans lequel

est un groupe de sous-formule (e).

13. Composé suivant l'une quelconque des revendications 1 à 7, dans lequel

est un groupe de sous-formule (f).

14. Composé suivant l'une quelconque des revendications 1 à 7, dans lequel

est un groupe de sous-formule (g).

15. Composé suivant la revendication 1, qui est :
la 2-(2-propoxyphényl)-pyrido-[2,3-d]-pyrimid-4(3H)-one,

la 2-(2-propoxyphényl)-pyrido-[3,4-d]-pyrimid-4(3H)-one,
la 2-(2-propoxyphényl)-pyrido-[4,3-d]-pyrimid-4(3H)-one,
la 2-(2-propoxyphényl)-pyrido-[3,2-d]-pyrimid-4(3H)-one,
la 2-(2-propoxyphényl)-ptéridin-4(3H)-one,
la 2-(2-propoxyphényl)-ptéridin-4,6(3H, 5H)-dione,
la 2-(2-propoxyphényl)-ptéridin-4, 6, 7(3H, 5H, 8H)-trione,
la 5,6-dihydro-3-méthylthio-5-oxo-7-(2-propoxyphényl)-pyrimido-[5,4-e] [1,2,4]-triazine,
la 3-amino-5,6-dihydro-5-oxo-7-(2-propoxyphényl)-pyrimido-[5,4-e] [1,2,4]-triazine,
la 5,6-dihydro-3-méthylamino-5-oxo-7-(2-propoxyphényl)-pyrimido-[5,4-e] [1,2,4]-triazine,
la 5,6-dihydro-3-méthoxy-5-oxo-7-(2-propoxyphényl)-pyrimido-[5,4-e] [1,2,4]-triazine,
la 3-méthylthio-8-oxo-6-(2-propoxyphényl)-7,8-dihydropyrimido-[4,5-e] [1,2,4]-triazine,
la 3-amino-8-oxo-6-(2-propoxyphényl)-7,8-dihydropyrimido-[4,5-e] [1,2,4]-triazine,
la 3-méthylamino-8-oxo-6-(2-propoxyphényl)-7,8-dihydropyrimido-[4,5-e] [1,2,4]-triazine,
la 3-méthoxy-8-oxo-6-(2-propoxyphényl)-7,8-dihydropyrimido-[4,5-e] [1,2,4]-triazine,
la 3,8-dioxo-6-(2-propoxyphényl)-3,4,7,8-tétrahydropyrimido-[4,5-e] [1,2,4]-triazine,
la 3-diméthylaminothio-8-oxo-6-(2-propoxyphényl)-7,8-dihydropyrimido-[4,5-e] [1,2,4]-triazine,
la 3-méthylthio-8-oxo-6-(2-allyloxyphényl)-7,8-dihydropyrimido-[4,5-e] [1,2,4]-triazine,
la 3-méthylthio-8-oxo-6-(2-isobutoxyphényl)-7,8-dihydropyrimido-[4,5-e] [1,2,4]-triazine,
la 3-méthylthio-8-oxo-6-(2-cyclopropylméthoxyphényl)-7,8-dihydropyrimido-[4,5-e] [1,2,4]-triazine ou
la 3-méthylthio-8-oxo-6-(2-méthoxyphényl)-7,8-dihydropyrimido-[4,5-e] [1,2,4]-triazine,

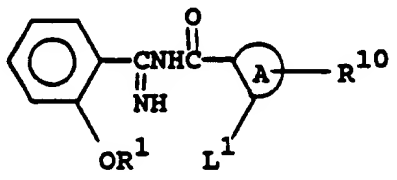
ou un sel de celles-ci acceptable du point de vue pharmaceutique.

16. Composé suivant l'une quelconque des revendications 1 à 15 utilisable comme médicament.

17. Composition pharmaceutique qui comprend un composé suivant l'une quelconque des revendications 1 à 15 et un support acceptable du point de vue pharmaceutique.

18. Procédé pour la préparation d'un composé de formule (1) ou d'un sel de celui-ci acceptable du point de vue pharmaceutique suivant la revendication 1, qui comprend :

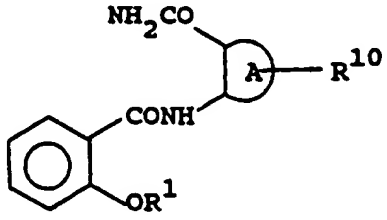
(a) la cyclisation d'un composé de formule (2) :



(2)

dans laquelle L^1 est un groupe pouvant être déplacé, R^1 et sont tels que définis dans la revendication 1, et R^{10} est un groupe R^2 tel que défini dans la revendication 1, ou un précurseur de celui-ci; ou

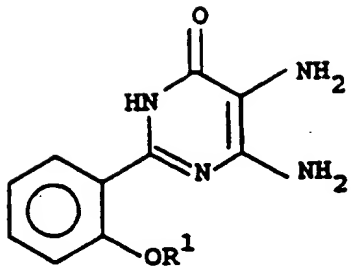
(b) la cyclisation d'un composé de formule (3) :



(3)

dans laquelle R^1, R^{10} et sont tels que définis plus haut;

(c) pour les composés dans lesquels R^2 et R sont chacun un atome d'hydrogène, la réaction d'un composé de formule (4) telle que définie plus haut, avec un glyoxal :



(4)

dans laquelle R^1 est tel que défini plus haut;

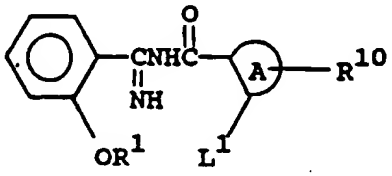
(d) pour les composés dans lesquels R^2 est un groupe 6-hydroxy et R est un atome d'hydrogène, la réaction d'un composé de formule (4) telle que définie plus haut, avec du chloral;

(e) pour les composés dans lesquels R^2 et R sont chacun un groupe hydroxy, la réaction d'un composé de formule (4) telle que définie plus haut, avec $(COL)_2$ dans lequel L est un groupe mobile;

et ensuite, si cela est nécessaire :

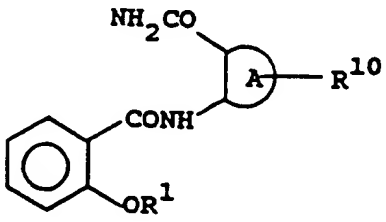
- la conversion d'un groupe R^{10} en un groupe R^2:
- la formation éventuelle d'un sel acceptable du point de vue pharmaceutique.

19. Composé de formule (2) telle que définie dans la revendication 18 :



(2)

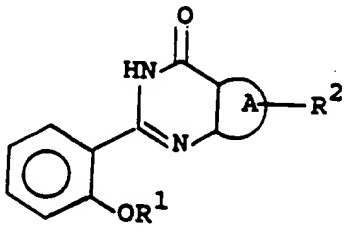
20. Composé de formule (3) telle que définie dans la revendication 18 :



(3)

Revendications pour l'Etat contractant suivant : ES

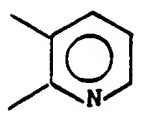
1. Procédé pour la préparation d'un composé de formule (1):



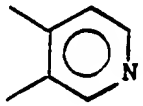
(1)

ou d'un sel de celui-ci acceptable du point de vue pharmaceutique, dans laquelle :

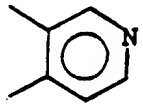
est un noyau représenté par les sous-formules (a), (b), (c), (d), (e), (f) ou (g) :



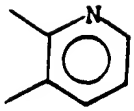
(a)



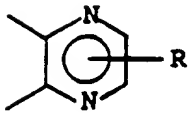
(b)



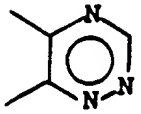
(c)



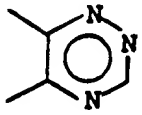
(d)



(e)



(f)



(g),

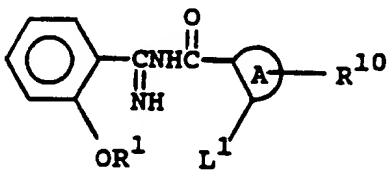
R^1 est un groupe alkyle en C_{1-6}, alcényle en C_{2-6}, cycloalkyl(en C_{3-5})-alkyle en C_{1-6} ou alkyle en C_{1-6} substitué par 1 à 6 atomes de fluor;

R^2 est un groupe alkylthio en C_{1-6}, alkylsulfonyle en C_{1-6}, alcoxy en C_{1-6}, hydroxy, atome d'hydrogène, groupe hydrazino, alkyle en C_{1-6}, phényle, $-NHCOR^3$ dans lequel R^3 est un atome d'hydrogène ou un groupe alkyle en C_{1-6}, ou $-NR^4R^5$, dans lequel R^4 et R^5 forment avec l'atome d'azote auquel ils sont attachés un groupe pyrrolidino, pipéridino, hexahydroazépino, morpholino ou pipérazino; ou bien R^4 et R^5 sont indépendamment un atome d'hydrogène, un groupe cycloalkyle en C_{3-5} ou alkyle en C_{1-6} qui est éventuellement substitué par $-CF_3$, phényle, $-S(O)_n$-alkyle en C_{1-6} dans lequel n est 0, 1 ou 2, $-OR^6$, $-CO_2R^7$ ou $-NR^8R^9$ dans lesquels R^6 à R^9 sont indépendamment un atome d'hydrogène ou un groupe alkyle en C_{1-6}, à condition que l'atome de carbone adjacent à l'atome d'azote ne soit pas substitué par ces groupes $-S(O)_n$-alkyle en C_{1-6}, $-OR^6$ ou $-NR^8R^9$; et

R est un atome d'hydrogène et peut aussi être un groupe hydroxy lorsque R^2 est un groupe hydroxy;

lequel procédé comprend :

(a) la cyclisation d'un composé de formule (2) :

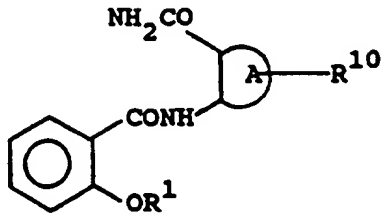


(2)

dans laquelle L^1 est un groupe pouvant être déplacé, R^1 et

sont tels que définis plus haut, et R^{10} est un groupe R^2 tel que défini plus haut, ou un précurseur de celui-ci; ou

(b) la cyclisation d'un composé de formule (3) :

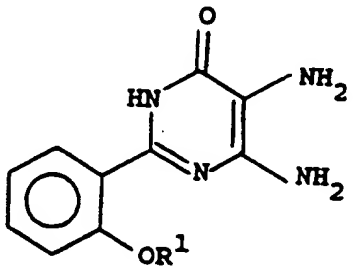


(3)

dans laquelle R^1, R^{10} et

sont tels que définis plus haut;

(c) pour les composés dans lesquels R^2 et R sont chacun un atome d'hydrogène, la réaction d'un composé de formule (4) telle que définie plus haut, avec un glyoxal :



(4)

dans laquelle R^1 est tel que défini plus haut;

(d) pour les composés dans lesquels R^2 est un groupe 6-hydroxy et R est un atome d'hydrogène, la réaction d'un composé de formule (4) telle que définie plus haut, avec du chloral;

(e) pour les composés dans lesquels R^2 et R sont chacun un groupe hydroxy, la réaction d'un composé de formule (4) telle que définie plus haut, avec $(COL)_2$ dans lequel L est un groupe mobile;

et ensuite, si cela est nécessaire :

- la conversion d'un groupe R^{10} en un groupe R^2:
- la formation éventuelle d'un sel acceptable du point de vue pharmaceutique.

2. Procédé suivant la revendication 1, pour préparer un composé dans lequel R^1 est un groupe alkyle en $_{2-5}$.

3. Procédé suivant la revendication 1, pour préparer un composé dans lequel R^1 est un groupe n-propyle.

4. Procédé suivant les revendications 1 à 3, pour préparer un composé dans lequel R^2 est un groupe alkylthio en C_{1-6}, alkylsulfonyle en C_{1-6} ou alcoxy en C_{1-6}.

5. Procédé suivant les revendications 1 à 3, pour préparer un composé dans lequel R^2 est un atome d'hydrogène, un groupe hydroxy ou hydrazino.

6. Procédé suivant les revendications 1 à 3, pour préparer un composé dans lequel R^2 est un groupe phényle ou alkyle en C_{1-6}.

7. Procédé suivant les revendications 1 à 3, pour préparer un composé dans lequel R^2 est un groupe $-NHCOR^3$ ou $-NR^4R^5$.

8. Procédé suivant les revendications 1 à 7, pour préparer un composé dans lequel

est un groupe de sous-formule (a).

9. Procédé suivant les revendications 1 à 7, pour préparer un composé dans lequel

est un groupe de sous-formule (b).

10. Procédé suivant les revendications 1 à 7, pour préparer un composé dans lequel

est un groupe de sous-formule (c).

11. Procédé suivant les revendications 1 à 7, pour préparer un composé dans lequel

est un groupe de sous-formule (d).

12. Procédé suivant les revendications 1 à 7, pour préparer un composé dans lequel

est un groupe de sous-formule (e).

13. Procédé suivant les revendications 1 à 7, pour préparer un composé dans lequel

est un groupe de sous-formule (f).

14. Procédé suivant les revendications 1 à 7, pour préparer un composé dans lequel

est un groupe de sous-formule (g).

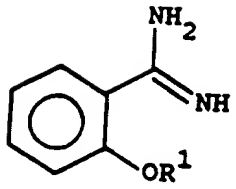
15. Procédé suivant la revendication 1, pour préparer un composé qui est :
la 2-(2-propoxyphényl)-pyrido-[2,3-d]-pyrimid-4(3H)-one,
la 2-(2-propoxyphényl)-pyrido-[3,4-d]-pyrimid-4(3H)-one,
la 2-(2-propoxyphényl)-pyrido-[4,3-d]-pyrimid-4(3H)-one,
la 2-(2-propoxyphényl)-pyrido-[3,2-d]-pyrimid-4(3H)-one,
la 2-(2-propoxyphényl)-ptéridin-4(3H)-one,
la 2-(2-propoxyphényl)-ptéridin-4,6(3H, 5H)-dione,
la 2-(2-propoxyphényl)-ptéridin-4, 6, 7(3H, 5H, 8H)-trione,
la 5,6-dihydro-3-méthylthio-5-oxo-7-(2-propoxyphényl)-pyrimido-[5,4-e] [1,2,4]-triazine,
la 3-amino-5,6-dihydro-5-oxo-7-(2-propoxyphényl)-pyrimido-[5,4-e] [1,2,4]-triazine,
la 5,6-dihydro-3-méthylamino-5-oxo-7-(2-propoxyphényl)-pyrimido-[5,4-e] [1,2,4]-triazine,
la 5,6-dihydro-3-méthoxy-5-oxo-7-(2-propoxyphényl)-pyrimido-[5,4-e] [1,2,4]-triazine,
la 3-méthylthio-8-oxo-6-(2-propoxyphényl)-7,8-dihydropyrimido-[4,5-e] [1,2,4]-triazine,
la 3-amino-8-oxo-6-(2-propoxyphényl)-7,8-dihydropyrimido-[4,5-e] [1,2,4]-triazine,
la 3-méthylamino-8-oxo-6-(2-propoxyphényl)-7,8-dihydropyrimido-[4,5-e] [1,2,4]-triazine,
la 3-méthoxy-8-oxo-6-(2-propoxyphényl)-7,8-dihydropyrimido-[4,5-e] [1,2,4]-triazine,
la 3,8-dioxo-6-(2-propoxyphényl)-3,4,7,8-tétrahydropyrimido-[4,5-e] [1,2,4]-triazine,
la 3-diméthylaminothio-8-oxo-6-(2-propoxyphényl)-7,8-dihydropyrimido-[4,5-e] [1,2,4]-triazine,
la 3-méthylthio-8-oxo-6-(2-allyloxyphényl)-7,8-dihydropyrimido-[4,5-e] [1,2,4]-triazine,
la 3-méthylthio-8-oxo-6-(2-isobutoxyphényl)-7,8-dihydropyrimido-[4,5-e] [1,2,4]-triazine,
la 3-méthylthio-8-oxo-6-(2-cyclopropylméthoxyphényl)-7,8-dihydro-pyrimido-[4,5-e] [1,2,4]-triazine
ou
la 3-méthylthio-8-oxo-6-(2-méthoxyphényl)-7,8-dihydropyrimido-[4,5-e] [1,2,4]-triazine,
ou un sel de celles-ci acceptable du point de vue pharmaceutique.

16. Procédé suivant la revendication 1, dans lequel L^1 est un atome d'halogène.

17. Procédé suivant la revendication 1, dans lequel L est un groupe alcoxy en C_{1-6} ou un atome d'halogène.

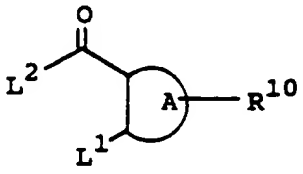
18. Procédé pour préparer une composition pharmaceutique, qui comprend la mise en association d'un composé de formule (1) suivant l'une quelconque des revendications 1 à 15 et d'un support acceptable du point de vue pharmaceutique.

19. Procédé pour préparer un composé de formule (2) telle que définie dans la revendication 1, qui comprend la réaction d'un composé de formule (5) :



(5)

dans laquelle R^1 est tel que défini dans la revendication 1,
avec un composé de formule (6) :

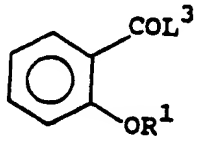


(6)

dans laquelle L^2 est un groupe mobile et L^1, R^{10} et

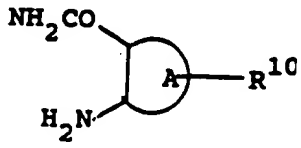
sont tels que définis dans la revendication 1.

20. Procédé pour préparer un composé de formule (3) telle que définie dans la revendication 1, qui comprend la réaction d'un composé de formule (7) :



(7)

dans laquelle R^1 est tel que défini dans la revendication 1 et R^3 est un atome d'halogène,
avec un composé de formule (8) :



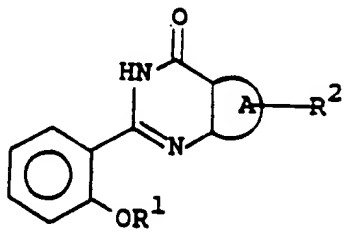
(8)

dans laquelle R^{10} et

sont tels que définis dans la revendication 1.

Revendications pour l'Etat contractant suivant : GR

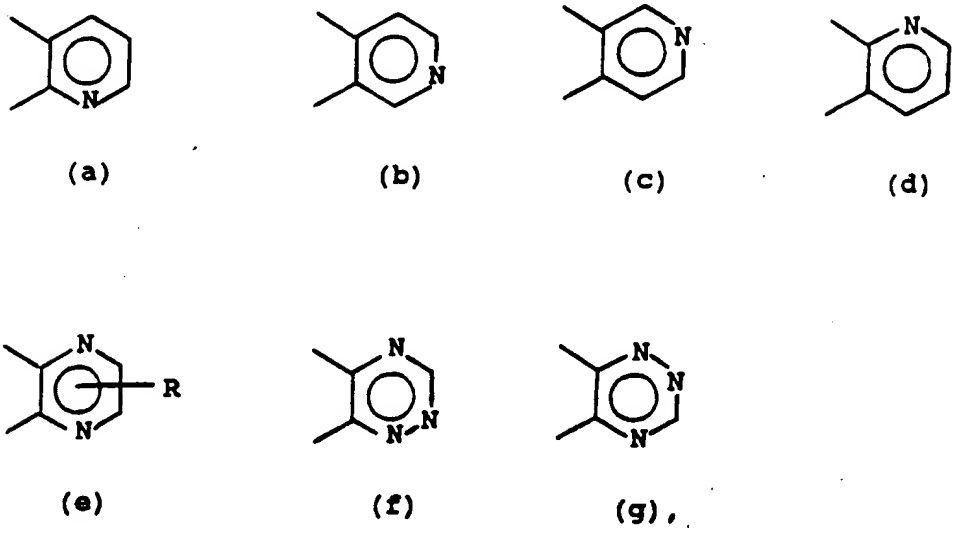
1. Procédé pour la préparation d'un composé de formule (1):



(1)

ou d'un sel de celui-ci acceptable du point de vue pharmaceutique, dans laquelle :

est un noyau représenté par les sous-formules (a), (b), (c), (d), (e), (f) ou (g) :



(a) (b) (c) (d)

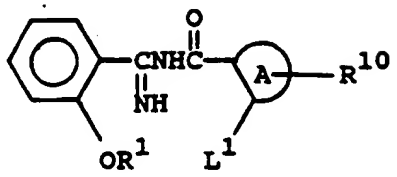
(e) (f) (g),

R^1 est un groupe alkyle en C_{1-6}, alcényle en C_{2-6}, cycloalkyl(en C_{3-5})-alkyle en C_{1-6} ou alkyle en C_{1-6} substitué par 1 à 6 atomes de fluor;

R^2 est un groupe alkylthio en C_{1-6}, alkylsulfonyle en C_{1-6}, alcoxy en C_{1-6}, hydroxy, atome d'hydrogène, groupe hydrazino, alkyle en C_{1-6}, phényle, $-NHCOR^3$ dans lequel R^3 est un atome d'hydrogène ou un groupe alkyle en C_{1-6}, ou $-NR^4R^5$, dans lequel R^4 et R^5 forment avec l'atome d'azote auquel ils sont attachés un groupe pyrrolidino, pipéridino, hexahydroazépino, morpholino ou pipérazino; ou bien R^4 et R^5 sont indépendamment un atome d'hydrogène, un groupe cycloalkyle en C_{3-5} ou alkyle en C_{1-6} qui est éventuellement substitué par $-CF_3$, phényle, $-S(O)_n$-alkyle en C_{1-6} dans lequel n est 0, 1 ou 2, $-OR^6$, $-CO_2R^7$ ou $-NR^8R^9$ dans lesquels R^6 à R^9 sont indépendamment un atome d'hydrogène ou un groupe alkyle en C_{1-6}, à condition que l'atome de carbone adjacent à l'atome d'azote ne soit pas substitué par ces groupes $-S(O)_n$-alkyle en C_{1-6}, $-OR^6$ ou $-NR^8R^9$; et

R est un atome d'hydrogène et peut aussi être un groupe hydroxy lorsque R^2 est un groupe

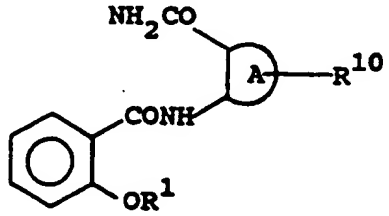
hydroxy;
lequel procédé comprend :
(a) la cyclisation d'un composé de formule (2) :



(2)

dans laquelle L^1 est un groupe pouvant être déplacé, R^1 et

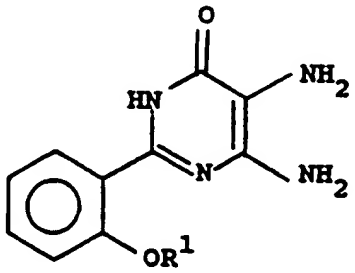
sont tels que définis plus haut, et R^{10} est un groupe R^2 tel que défini plus haut, ou un précurseur de celui-ci; ou
(b) la cyclisation d'un composé de formule (3) :



(3)

dans laquelle R^1, R^{10} et

sont tels que définis plus haut;
(c) pour les composés dans lesquels R^2 et R sont chacun un atome d'hydrogène, la réaction d'un composé de formule (4) telle que définie plus haut, avec un glyoxal :



(4)

dans laquelle R^1 est tel que défini plus haut;
(d) pour les composés dans lesquels R^2 est un groupe 6-hydroxy et R est un atome d'hydrogène, la réaction d'un composé de formule (4) telle que définie plus haut, avec du chloral;

(e) pour les composés dans lesquels R^2 et R sont chacun un groupe hydroxy, la réaction d'un composé de formule (4) telle que définie plus haut, avec $(COL)_2$ dans lequel L est un groupe mobile;

et ensuite, si cela est nécessaire :

- la conversion d'un groupe R^{10} en un groupe R^2:
- la formation éventuelle d'un sel acceptable du point de vue pharmaceutique.

2. Procédé suivant la revendication 1, pour préparer un composé dans lequel R^1 est un groupe alkyle en $_{2-5}$.

3. Procédé suivant la revendication 1, pour préparer un composé dans lequel R^1 est un groupe n-propyle.

4. Procédé suivant les revendications 1 à 3, pour préparer un composé dans lequel R^2 est un groupe alkylthio en C_{1-6}, alkylsulfonyle en C_{1-6} ou alcoxy en C_{1-6}.

5. Procédé suivant les revendications 1 à 3, pour préparer un composé dans lequel R^2 est un atome d'hydrogène, un groupe hydroxy ou hydrazino.

6. Procédé suivant les revendications 1 à 3, pour préparer un composé dans lequel R^2 est un groupe phényle ou alkyle en C_{1-6}.

7. Procédé suivant les revendications 1 à 3, pour préparer un composé dans lequel R^2 est un groupe $-NHCOR^3$ ou $-NR^4R^5$.

8. Procédé suivant les revendications 1 à 7, pour préparer un composé dans lequel

est un groupe de sous-formule (a).

9. Procédé suivant les revendications 1 à 7, pour préparer un composé dans lequel

est un groupe de sous-formule (b).

10. Procédé suivant les revendications 1 à 7, pour préparer un composé dans lequel

est un groupe de sous-formule (c).

11. Procédé suivant les revendications 1 à 7, pour préparer un composé dans lequel

est un groupe de sous-formule (d).

12. Procédé suivant les revendications 1 à 7, pour préparer un composé dans lequel

est un groupe de sous-formule (e).

13. Procédé suivant les revendications 1 à 7, pour préparer un composé dans lequel

est un groupe de sous-formule (f).

14. Procédé suivant les revendications 1 à 7, pour préparer un composé dans lequel

est un groupe de sous-formule (g).

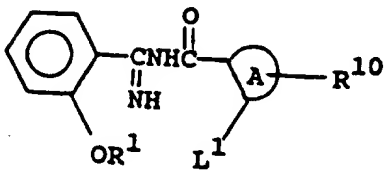
15. Procédé suivant la revendication 1, pour préparer un composé qui est :
la 2-(2-propoxyphényl)-pyrido-[2,3-d]-pyrimid-4(3H)-one,
la 2-(2-propoxyphényl)-pyrido-[3,4-d]-pyrimid-4(3H)-one,
la 2-(2-propoxyphényl)-pyrido-[4,3-d]-pyrimid-4(3H)-one,
la 2-(2-propoxyphényl)-pyrido-[3,2-d]-pyrimid-4(3H)-one,
la 2-(2-propoxyphényl)-ptéridin-4(3H)-one,
la 2-(2-propoxyphényl)-ptéridin-4,6(3H, 5H)-dione,
la 2-(2-propoxyphényl)-ptéridin-4, 6, 7(3H, 5H, 8H)-trione,
la 5,6-dihydro-3-méthylthio-5-oxo-7-(2-propoxyphényl)-pyrimido-[5,4-e] [1,2,4]-triazine,
la 3-amino-5,6-dihydro-5-oxo-7-(2-propoxyphényl)-pyrimido-[5,4-e] [1,2,4]-triazine,
la 5,6-dihydro-3-méthylamino-5-oxo-7-(2-propoxyphényl)-pyrimido-[5,4-e] [1,2,4]-triazine,
la 5,6-dihydro-3-méthoxy-5-oxo-7-(2-propoxyphényl)-pyrimido-[5,4-e] [1,2,4]-triazine,
la 3-méthylthio-8-oxo-6-(2-propoxyphényl)-7,8-dihydropyrimido-[4,5-e] [1,2,4]-triazine,
la 3-amino-8-oxo-6-(2-propoxyphényl)-7,8-dihydropyrimido-[4,5-e] [1,2,4]-triazine,
la 3-méthylamino-8-oxo-6-(2-propoxyphényl)-7,8-dihydropyrimido-[4,5-e] [1,2,4]-triazine,
la 3-méthoxy-8-oxo-6-(2-propoxyphényl)-7,8-dihydropyrimido[4,5-e] [1,2,4]-triazine,
la 3,8-dioxo-6-(2-propoxyphényl)-3,4,7,8-tétrahydropyrimido-[4,5-e] [1,2,4]-triazine,
la 3-diméthylaminothio-8-oxo-6-(2-propoxyphényl)-7,8-dihydropyrimido-[4,5-e] [1,2,4]-triazine,
la 3-méthylthio-8-oxo-6-(2-allyloxyphényl)-7,8-dihydropyrimido-[4,5-e] [1,2,4]-triazine,
la 3-méthylthio-8-oxo-6-(2-isobutoxyphényl)-7,8-dihydropyrimido-[4,5-e] [1,2,4]-triazine,
la 3-méthylthio-8-oxo-6-(2-cyclopropylméthoxyphényl)-7,8-dihydropyrimido-[4,5-e] [1,2,4]-triazine ou
la 3-méthylthio-8-oxo-6-(2-méthoxyphényl)-7,8-dihydropyrimido-[4,5-e] [1,2,4]-triazine,
ou un sel de celles-ci acceptable du point de vue pharmaceutique.

16. Procédé suivant la revendication 1, dans lequel L^1 est un atome d'halogène.

17. Procédé suivant la revendication 1, dans lequel L est un groupe alcoxy en C_{1-6} ou un atome d'halogène.

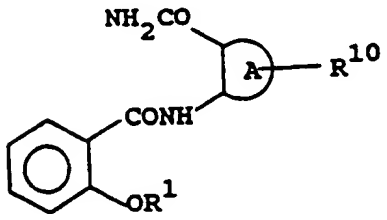
18. Procédé pour préparer une composition pharmaceutique, qui comprend la mise en association d'un composé de formule (1) suivant l'une quelconque des revendications 1 à 15 et d'un support acceptable du point de vue pharmaceutique.

19. Composé de formule (2) telle que définie dans la revendication 1 :



(2)

20. Composé de formule (3) telle que définie dans la revendication 1 :



(3)